

Syncope

An Evidence-Based Approach

Michele Brignole
David G. Benditt
Editors

Second Edition



Springer

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Foreword

The authors of this new edition of an evidence-based approach to syncope are all distinguished in their field. For example, since 2001, many of the authors have contributed to four consecutive evidence-based guidelines for the management of syncope, published by the European Society of Cardiology (ESC) and latterly the American College of Cardiology/American Heart Association/Heart Rhythm Society (2017). At each stage, gaps in evidence were identified and subsequent research evolved to inform future iterations. Consequently, these authors have taken this field to a new level of understanding and management, driven by the commitment of all but in particular, the ESC panel chairman and co-editor of this edition, Michele Brignole.

From a personal perspective, after setting up a dedicated UK syncope service in 1992, it became clear that syncope involved multiple disciplines, pertinent to all ages, for which at the time, there were no clear care pathways, training or education programmes. To all intents and purposes, syncope was a new ‘discipline’. Skills in aspects of cardiology, emergency medicine, internal medicine, physiology, neurology and autonomic diseases, geriatric medicine and paediatrics were required to cover the breadth of causes, cohorts and service models. In this regard, representation on the both the ESC and American syncope guidelines panels evolved to reflect this multidisciplinary, including the role of nursing in service delivery, coupled with new practical instructions on how to establish syncope services aimed at reducing hospitalizations, under- and misdiagnoses and costs of care.

Why Syncope? Syncope is one of the most common symptoms that physicians and health care services encounter; a lifetime prevalence of over 40%. Even very young children will experience episodes of apparent syncope. The incidence peaks between ages 10 and 30 and again after age 70 years. The majority of events are caused by well-recognized triggers and constitute the common ‘faint’—vasovagal syncope. Such patients may experience lifelong episodes which tend to cluster. These patients have a lower threshold for what is otherwise a normal physiological response—a response that humans and animals exhibit under situations of physiological stress (e.g., haemorrhage, emotional distress, etc.). Nonetheless, speedy recognition and management are important for these patients to curtail unnecessary

worry and costs including cost of care due to collapse-related injury. Alternatively, as detailed in this edition, syncope may be due to structural or arrhythmic cardiac disease or albeit infrequently certain neurological disorders necessitating alternative evidence-based approaches.

Given that syncope is responsible for up to 5% of emergency department visits, with varying hospitalization rates up to 40%, risk stratification in the ED setting is a priority and a new addition to this new edition. Even with comprehensive guidelines on either side of the Atlantic, there remains widespread disparity in the management of syncope. Excessive service utilization and associated costs are, in the main, due to inappropriate hospital admission and overzealous investigation.

One of the commonest challenges in the management of syncope and related disorders is the older patient, due to atypical presentations, difficulties in attaining witness accounts, variation in tolerance of medications and interventions and high rates of comorbidities. Ageing demographics are rapidly changing worldwide. For most of history, 3% of persons lived to 65 or over. Today 26% of Japanese, 20% of Europeans and 17% US citizens are over 65. The fastest population increase in the coming years will be in those over 80. Because of successful survival from midlife cardiovascular disorders and more aggressive management of cardiovascular disorders in this rapidly rising demographic, prevalence of syncope and related disorders are increasing and will continue to rise. This challenge may be addressed by new strategies for personalized interventions, as yet unresolved.

Who is responsible for the discipline of Syncope? Despite evidence for benefits to the individual and health care systems of a structured approach to syncope, the development of comprehensive services, as recommended by the guidelines, is not yet widespread. Because of the multidisciplinary nature of syncope, no single speciality currently has responsibility for training and education. Consequently, as training schemes for individual disciplines have become more streamlined and structured, responsibility for certification of clinicians for syncope remains undetermined. Other barriers include disparity in cost structures in different health care systems, which influence drivers for new services. Until these are resolved, we recommend that a leader from any pertinent specialty should engage with local stakeholders and employ a care model which best fits local needs and systems with privileged access to sub-specialities as necessary; these concepts are reflected in this new edition.

One of my great personal pleasures, as we have progressed syncope management over the past number of years, is the cross country collaborations, close partnerships and friendships that have developed. The authors of this new edition are committed experts and collaborators who herewith present a refreshed and pragmatic approach to syncope, embedded in evidence but highlighting, where relevant, gaps in evidence. We encourage the new generations to engage with this fascinating field.

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Preface

Rationale for the Second Edition

The First Edition of this book was published in 2011. Utilizing an evidence-based approach, it offered practical guidance for the wide range of medical practitioners involved in the care of patients who present with transient loss of consciousness.

This Second Edition was initiated after publication (in the years 2017 and 2018, respectively) of the new American and the most recent European guidelines on the management of syncope and collapse. The editors, both of whom participated as contributing guidelines authors, realized that there were in the latest guideline recommendations enough new concepts to justify an updated edition of the book. Although, not unexpectedly, when dealing with comparable topics, most of the recommendations within the two practice guidelines are very similar to each other, there are some interesting differences that are worthy of discussion. Additionally, there remain certain unresolved topics that merit being addressed. Thus, the second edition has several goals: (1) to offer a multidisciplinary update taking advantage of the best evidence provided by the two recent guidelines, (2) to provide explanation and practical advice for those issues in which the two guidelines differ and (3) to highlight where solid information is lacking and towards which further research may be profitably directed.

Since syncope and collapse are very common clinical problems in need of multidisciplinary consideration, the editors have assembled a team of key opinion leaders in the study and management of syncope/collapse which is not only international in nature but also represents a wide range of specialties including cardiology, neurology, internal medicine, emergency medicine and geriatrics. Many of the authors participated as members of the task forces that not only wrote the guidelines mentioned above but have also contributed to the critical and growing research foundations of the field. We are grateful to all of them for their voluntary, timely and unconditional support.

While all the chapters of the First Edition were written by the two editors, in this Second Edition each chapter has been written by individuals who have

demonstrated interest and expertise in the specific topic being addressed. The editors prepared the table of contents, defined the format and reviewed the chapters in order to minimize inconsistencies and duplication while at the same time allowing for differences of opinion where that was deemed appropriate. A diverse geographical distribution was purposely sought in order to achieve balanced conclusions. The table of contents differs substantially from the first edition; specifically, while some chapters required primarily deep revision and update of their content, many others are completely new.

Aims and Scope

Syncope/collapse has many possible causes, and a multidisciplinary approach is most effective for evaluation and treatment. Often the expertise of cardiologists, neurologists, emergency medicine specialists, general practitioners, geriatricians and other clinicians is needed; the critical need for broad-ranging expertise is emphasized herein. However, unfortunately, each of these sub-specialties has tended to develop and use different terminology, methodology and management guidelines; these differences have complicated effective interaction among the various caregivers and have made evaluation and treatment of affected patients more complex. One of the aims of this Second Edition is to try to provide a viewpoint that can be adopted effectively across specialties.

In summary, this volume represents a comprehensive multidisciplinary review of the subject, offering recommendations based on the most recently published practice guidelines as well as experience derived from the various sub-specialties. It begins by discussing the scientific basis behind the diverse pathophysiology of conditions that may cause syncope/collapse and reviews optimal clinical management pathways. Later sections of the book then take a more practical approach, defining recommendations for the practice of syncope/collapse management. The most common procedures and tests are discussed along with their indications, methodology, interpretation and limitations.

The Second Edition has been designed to fulfil the needs of the wide range of medical practitioners involved in the care of syncope/collapse patients. All specialties will benefit from the concentration on the importance of medical history taking. Emergency room physicians and internists will be aided by the focus on the initial evaluation and risk stratification. The general practitioner will be aided in the care of their patients by the focus on the initial history taking and advice regarding the most appropriate initial tests and avoidance of low yield diagnostic procedures. Cardiologists and cardiac electrophysiologists will find up-to-date recommendations regarding the indications for and appropriate interpretation of non-invasive and invasive cardiac testing. Finally, geriatricians, neurologists and psychiatrists will find useful the sections exploring the often-difficult topic of distinguishing true syncope from other important conditions that may present as transient loss of consciousness or mimics of transient loss of consciousness.

In closing, the editors wish to thank their many friends and colleagues (and especially those who served on the major professional society Syncope Guidelines Committees) for their crucial input through invaluable discussions and debates over many years. These individuals have educated us and influenced our thinking; inevitably their ideas and contributions have made their way into and substantially improved this work.

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Part I
TLOC/Collapse: Pathophysiologic and
Epidemiologic Features

Chapter 1

Syncope: Definition and Classification-Contrasting the American and European Guidelines



Noah N. Williford and Brian Olshansky

A cogent definition of syncope is critical to understand its causes, to elucidate its mechanisms, and to develop an approach to management. From a clinical standpoint, unless a carefully constructed definition is present, the problem becomes difficult to categorize and understand. The European Society of Cardiology (ESC) and, independently, the American College of Cardiology, American Heart Association, Heart Rhythm Society (ACC/AHA/HRS) formalized definitions for syncope as part of two recent independent guidelines written by completely different authors, experts, and investigators who had considered the entirety of the literature and scope of the problem [1, 2]. Here, we review, and contrast, definitions of syncope set forth by the ESC and the AHA/ACC/HRS guidelines as they both considered syncope in lieu of other conditions that lead to transient loss of consciousness, other altered states of consciousness, coma, collapse, and falls [3]. We then consider approaches to classification of syncope as described in each guideline and address some of the gaps and nuances that make the problem of syncope nebulous as a symptom but critical to understand clinically in order to evaluate, manage, and treat patients.

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1.1 What Is Consciousness?

Syncope represents a form of loss of consciousness. Before understanding loss of consciousness, there must be a reasonable understanding of consciousness is. Consciousness the state of being awake and aware of self and surroundings (see also the Chapter by van Dijk et al. chapter 2 in this volume). However, one is not necessarily unconscious when not awake and unaware of self and surroundings. Additionally, being conscious implies that one can interact with surroundings and respond to stimuli. Those who are asleep may respond to stimuli whether or not they remember doing so.

Complete loss of consciousness includes the inability or lack of awareness to perceive, think, and understand. Individuals who are unconscious cannot, and do not, respond to any stimuli and are unable to understand those stimuli. An individual might not be aware that they are responding, but do respond, making consciousness more difficult to comprehend. Additionally, consciousness is present even if there is disorientation or confusion, preventing the ability to respond. These issues make loss of consciousness difficult but important to categorize, as medications, intoxication, dementia, stroke, coma, seizures, and other issues, including sleep, can cause alterations in consciousness and these must be distinguished from syncope. Particularly perplexing is pseudo-syncope or pseudo-seizures in which the state of consciousness is unclear, or at least may reasonably be debated.

Neurobiological phenomena responsible for consciousness are becoming better understood. Multiple areas of the brain have been implicated; in particular, the reticular activating system (RAS) appears to be critical to generate consciousness. Functional MRI studies indicate that white matter tracts integrating various parts of the brain may be important, and that the thalamo-cortical and cortico-cortical tracts are likely involved. Temporal and spatial integration amid increasing entropy provide a diversity of transmitted information seemingly necessary for consciousness [4].

Anesthetics, such as propofol, functionally disconnect the posterior parietal cortex from other cortical regions and may cause loss of consciousness due to functional loss of brain integration [5]. Anesthetic unconsciousness can also be associated with deactivation of the mesial-parietal cortex, posterior cingulate gyrus, and precuneus. Integration of information between different brain regions may be the underpinnings of consciousness [6]. Other areas such as the midbrain, the rostral pons, and the thalamus may be critical as well, but global reduction in cerebral blood flow might not be necessary to create total loss of consciousness.

Understanding what affects, impairs, or enhances consciousness remains an inexact science, but loss of blood flow to critical regions in the brain alters consciousness. Loss of consciousness can be transient, lasting a few seconds or minutes, be persistent, or become permanent. Transient loss of consciousness (TLOC) with complete return to normal cerebral functioning is due to a reversible process and has an immense list of causes.

1.2 Transient Loss of Consciousness

In the ACC/AHA/HRS guidelines, loss of consciousness is considered a cognitive state in which one lacks awareness of oneself in a given situation such that there is an inability to respond to stimuli. Transient loss of consciousness (TLOC) may be self-limited but it is not necessarily syncope, as other conditions, including functional disorders (e.g., pseudo-syncope or pseudo-seizures), seizures, hypoglycemia, metabolic derangements, and drug or alcohol intoxication, can result in TLOC. The list of causes for TLOC also includes: coma, head trauma, intracerebral hemorrhage, stroke, and many other conditions. These conditions are separate from syncope as they lead to a prolonged period in which responsiveness is not present and yet they can occasionally be difficult to distinguish from TLOC due to syncope.

TLOC can be divided into syncope and non-syncope related conditions (Fig. 1.1). With syncope, the underlying mechanism is presumed to be transient cerebral hypoperfusion, whereas non-syncope causes have different mechanisms. Both guidelines agree that a detailed history is the most essential component to determine whether or not TLOC occurred and whether it was due to syncope or not. After recovering from syncope, patients may endorse premonitory symptoms of “pre-syncope” including weakness, nausea, palpitations, lightheadedness, and visual changes, followed by “waking up on the ground” if they were previously standing. These symptoms can be helpful to determine the cause for syncope in some instances. Patients who experience syncope, without a prodrome, or while supine or prone, should raise concern for a serious cause, particularly a cardiac arrhythmia.

Some patients are unable to give a detailed history. In such cases, eyewitness accounts can be invaluable. TLOC and syncope are often unwitnessed, and witnesses can be unreliable whether or not they have medical expertise. The ESC guidelines directly address this issue, giving a class IIa recommendation (“should be considered”) to home video recordings such as is possible with many cell phones.

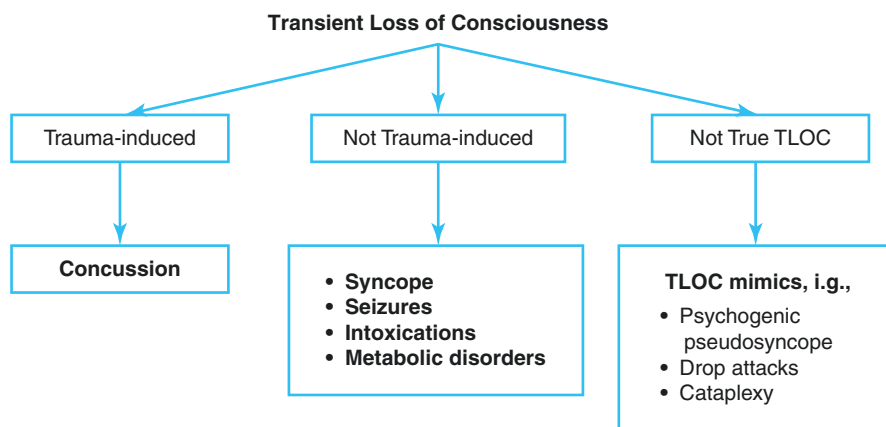


Fig. 1.1 TLOC differential diagnosis (from European Society of Cardiology Guidelines)

While the ACC/AHA/HRS guidelines state the importance of distinguishing syncope from other forms of TLOC, the ESC guidelines categorize causes of TLOC, and offer distinguishing features of these causes. The ESC guidelines recommend first dividing TLOC into traumatic and non-traumatic. If deemed non-traumatic TLOC, the next step is to differentiate between syncope, seizures, and psychogenic causes. The traumatic causes are not considered further but a person may experience syncope, and then experience head trauma; the latter may potentially mask the syncope episode, and only the availability of eye-witness accounts may clarify the sequence of events.

When considering TLOC, there can be very prolonged episodes with confusion before or after the episode and rapid or slow recovery neurologically. In the ESC guidelines, syncope is considered to be a state of real or apparent loss of consciousness with loss of awareness and characterization of “amnesia” during the period of unconsciousness with abnormal motor control and loss of responsiveness of short duration. The definition of short duration is unclear and there is no specific definition of loss of postural tone. Abnormal motor control opens up the potential differential to seizures and conditions such as stroke. It is clear from the ESC and the ACC/AHA/HRS guidelines that definitions are often based on the history taken from the patient and eyewitnesses, as well as based on prior records. Of course, eyewitnesses may vary in what they see, and the patient’s experience may or may not indicate what actually occurred during the episode. Therefore, all TLOC needs to be thoroughly scrutinized employing information from the patient as well as bystanders before labelling the TLOC event as syncope.

While syncope is defined by the characteristics stated, the lack of hard and fast rules for some of these characteristics creates the potential for overlap with other conditions. Many things can cause loss of consciousness including seizure, coma, head trauma, intracerebral hemorrhage, stroke, and hypoglycemia. These conditions are distinct from syncope as a prolonged period of non-responsiveness is present, yet, they need to be considered in the differential diagnosis. Additionally, an individual with altered consciousness may be unaware of their environment, and believe that they have lost consciousness, while to an observer, they appear conscious.

To confuse matters even more, syncope and “collapse” are often considered together. There is reason for this; both conditions can appear to be similar. Further, syncope is often considered with collapse as part of the Combined Medicaid Medicare Services (CMS) Diagnosis-Related Group (DRG) in the USA. On the other hand, collapse can actually represent an aborted cardiac arrest due to ventricular tachycardia, for example. Collapse in this circumstance can cause TLOC due to cerebral hypoperfusion but it tends to have dire consequences.

1.3 Terminology

A clear, well-developed, definition of syncope is critical to understand the TLOC/syncope/collapse problem and its causes, to formulate an approach to evaluation and risk management, and to guide diagnostic or therapeutic intervention. It is no

surprise, therefore, that the AHA/ACC/HRS guidelines and the ESC guidelines incorporate clear-cut definitions of syncope, exclusion of associated conditions and classification of potential etiologies in a broad-based fashion.

1.4 Syncope: Definitions

Syncope is a form of TLOC thought to be due to cerebral hypoperfusion, characterized by rapid onset, short duration, and spontaneous recovery. The ACC/AHA/HRS generally agrees with the ESC definition. Let us break down the definition into its components:

Transient Transient implies that the loss of consciousness has a defined beginning and a defined end. The defined end implies that the person returns to baseline awareness. The fact that resolution occurs suggests that no permanent damage has occurred. Thus, conditions that cause damage and lasting impaired consciousness are not syncope unless of course ensuing trauma due to the episode was responsible.

Rapid Onset While most patients and witnesses are unable to give a clear timeline of events, the onset of syncope is relatively rapid. However, there is no formal time-frame definition of “rapid” in either guideline document, and thus, “rapid onset” is subjective. When pre-syncope symptoms occur, overt syncope typically occurs within 20 seconds, however.

Recovery is Spontaneous, Complete, and Usually Prompt This criterion differentiates syncope from conditions such as trauma, stroke, seizure, and drugs that do not briskly reverse on their own and may even require intervention; it also helps distinguish syncope from aborted cardiac arrest. It is important to note, however, that some forms of syncope such as vasovagal syncope may be characterized by a period of fatigue after resolution of the event. These symptoms contrast to the “post-ictal” state after a seizure. No time frame given by either guideline documents “prompt.”

Underlying Mechanism: Transient Global Cerebral Hypoperfusion Other non-syncope causes of TLOC (which may even resolve quickly and spontaneously) involve other mechanisms. For example, trauma results in TLOC due to the effect of the direct trauma, seizures result from inappropriate electrical discharges in the brain, and stroke from direct damage to the brain. In contrast, true syncope results from transient cerebral hypoperfusion. However, global cerebral hypoperfusion may not be necessary, as only select areas of the brain may be necessary for consciousness. In addition, there are functional conditions such as “psychogenic pseudo-syncope” for which mechanisms of TLOC are not fully understood but the individual appears unresponsive and yet there is no evidence of cerebral hypoperfusion. Perhaps other mechanisms are responsible for TLOC rather than transient cerebral hypoperfusion. Rarely is the patient with syncope proven to have transient cerebral hypoperfusion—it is just assumed.

1.5 What Caused the “Spell”?

Patients do not typically endorse a chief complaint of “syncope” when they present for evaluation (Table 1.1). In English speaking countries, patients and witnesses are more likely to use terms such as “faint,” “blackout,” “spell,” “collapse,” “fit,” or “seizure” [7]. When such phrases are used, it is up to the astute physician to determine if syncope truly occurred. In fact, it can be difficult to distinguish among various terms such as “spells,” transient confusion, weakness, dizziness, loss of memory, lightheadedness, falling episodes, coma, sleeping, confusion, intoxication from fainting in some instances. An elderly patient, already confused, may fall and then lose consciousness transiently from head trauma with no recall of the event. On the other hand, the same individual could pass out, then fall, and become confused from the ensuing head trauma. Diverse, real life, clinical presentations can be perplexing.

1.6 Classification

While all syncope is secondary to a decrease in cerebral perfusion, there are many potential mechanisms and etiologies. Thus, both guidelines provide a classification system. The European guidelines attempt to classify disorders based on common pathophysiology, presentation and risk. Table 1.2 provides the ESC classification. ESC categorizes syncope in to one of the three etiologies: reflex (neurally-mediated) syncope, syncope due to orthostatic hypotension (OH), and cardiac syncope. Previous iterations of the guidelines separated cardiac syncope into “primary arrhythmias” and “structural cardiovascular disease.” However, these 2 subgroups have since been combined and are categorized more generally as cardiac syncope. Previous iterations also include rare “cerebrovascular and neurologic causes.” These conditions are now considered mimickers of true syncope.

Conversely, the ACC/AHA/HRS guidelines place importance on two categories: cardiac and non-cardiac syncope. The rationale behind this initial categorization is that cardiac causes are potentially lethal, while non-cardiac causes are usually benign (if one excludes risk of injury). Once a syncopal episode has been deemed unlikely to be cardiac, further categorization is made within non-cardiac syncope and is similar to the ESC classifications. These categories are reflex (neurally-mediated), orthostatic hypotension, and other uncommon conditions. Rare etiologies are also noted.

1.6.1 *Reflex (Neurally-Mediated) Syncope*

Reflex (neurally-mediated) syncope goes by multiple names, but both guidelines prefer this term. Reflex syncope is due to a reflexive drop in peripheral vascular resistance leading to venous pooling with reduced stroke volume, and a complex

Table 1.1 Terms used to describe TLOC (some of which may be syncope)

<i>1. English (USA)</i>
– Blackout
– Collapse
– Faint
– Fit
– Spell
<i>2. English (UK)</i>
– Funny turns
– Giddiness
<i>3. Dutch</i>
– Flauw (weak /feeble/faint)
– Vallen (to fall) or “vallen flauw” (falling weak or becoming feeble)
– Aanval or (attack)
– Wegraking’ (becoming away)
<i>4. French</i>
– Evanouissement
– Perte de connaissance (loss of consciousness)
– Tomber dans les pommes (fall in the apples!)
<i>5. German</i>
– Bewußtlosigkeit (unconsciousness)
– Ich hatte einen “blackout” (I suffered from a “blackout”)
– Ich bin umgefallen (I had a collapse)
– Kollaps (collapse)
– Ohnmacht (without power, without control)
<i>6. Italian</i>
– Perdita Dei sensi (colloquial, means loss of sensorial functions)
– Perdita di conoscenza (colloquial and medical, loss of consciousness)
– Sincope (medical term, but sometimes colloquial)
– Svenimento (colloquial, means fainting)
<i>7. Japanese</i>
– Kiwo-ushinau (colloquial, loss of consciousness)
– Shisshin (medical term, syncope)
– Kizetsu (colloquial, loss of consciousness)
– Ishikisyougai (medical term, loss of consciousness)
<i>8. Spanish</i>
– Desmayo (syncope, mostly used for the most common vasovagal situations)
– Lipotimia (used probably for “common faint”; it really describes the typical vasovagal reaction with prodrome)
– Mareo (literally is closer to “dizziness,” and sometimes it means just “nausea,” but it can be also used to describe syncope)

Table 1.2 Classification of syncope

<i>Reflex (neurally-mediated) syncope</i>
Vasovagal
– Orthostatic VVS: Standing, less common sitting
– Emotional; fear, pain (somatic or visceral), instrumentation, blood phobia
Situational
– Micturition
– Gastrointestinal stimulation (swallow, defecation)
– Cough, sneeze
– Post-exercise
– Others (e.g., laughing, brass instrument playing)
Carotid sinus syndrome
Non-classical forms (without prodromes and/or without apparent triggers and/or atypical presentation)
<i>Syncope due to orthostatic hypotension (OH)</i>
<i>Note that hypotension may be exacerbated by venous pooling during exercise (exercise-induced), after meals (postprandial hypotension), and after prolonged bed rest (deconditioning)</i>
Drug-induced OH (most common cause of OH)
– e.g., vasodilators, diuretics, phenothiazine, antidepressants
Volume depletion
– Hemorrhage, diarrhea, vomiting, etc.
Primary autonomic failure (neurogenic OH):
– Pure autonomic failure, multiple system atrophy, Parkinson's disease, dementia with Lewy bodies
Secondary autonomic failure (neurogenic OH):
– Diabetes, amyloidosis, spinal cord injuries, auto-immune autonomic neuropathy, paraneoplastic autonomic neuropathy, kidney failure
<i>Cardiac syncope</i>
Arrhythmia as primary cause
Bradycardia
– Sinus node dysfunction (including bradycardia/tachycardia syndrome)
– Atrioventricular conduction system disease
Tachycardia
– Supraventricular
– Ventricular
Structural cardiac: Aortic stenosis, acute myocardial infarction/ischemia, hypertrophic cardiomyopathy, cardiac masses (atrial myxoma, tumors, etc.), pericardial disease/tamponade, congenital anomalies of coronary arteries, prosthetic valve dysfunction
Cardiopulmonary and great vessels: Pulmonary embolus, acute aortic dissection, pulmonary hypertension

variation of heart rate, or both, due to sympathetic withdrawal and/or vagal activation, usually contemporaneously, but not necessarily. Vasovagal syncope in an otherwise normal, healthy individual is the most common type of reflex syncope and is characterized by specific clinical features. These features include prolonged standing and pain/emotional stress as a trigger, a prodrome of warmth, diaphoresis, nausea, and pallor, and fatigue after the event. The prodrome is often less marked in older fainters.

Situational syncope is a second type of reflex syncope. However, it is differentiated by being specifically incited by a known trigger. Well-described triggers include micturition, coughing, sneezing, swallowing, or defecating. Both types of syncope occur in people of all ages, but this form is more common in older individuals.

There are many triggers of the neurally-mediated reflex which is also sometimes referred to as the neuro-cardiogenic reflex. These are not all benign. Acute inferior wall myocardial infarction, aortic stenosis, and hypertrophic cardiomyopathy as well as pulmonary emboli can trigger the Bezold-Jarisch Reflex which involves the same sympathetic and parasympathetic pathways believed associated with the neuro-cardiogenic reflex. The cause for this type of neurally-mediated syncope is not always more benign. This also leads to an overlap between the apparent benign causes for syncope which appeared to be neurally-mediated and the more malignant forms that tend to be cardiac. Importantly, the mechanism for these reflexes are not completely understood.

A third type of reflex (neurally-mediated) syncope is carotid sinus syndrome (CSS). In this type, mechanical stimulation of the carotid sinus causes a cardioinhibitory and vasodepressor response involving one or multiple of the following: brief asystole, AV block, systemic vasodilation. CSS tends to occur in older males and may be associated with the higher burden of cardiovascular disease.

Reflex (neurally-mediated) syncope can often be diagnosed based on history and physical exam alone (including orthostatic vital signs and ECG). The ACC/AHA/HRS guidelines give the diagnostic value of the history and physical examination a class I recommendation. The ESC guidelines do not give a specific recommendation, but state that history and physical exam are important. Unfortunately, not all patients can provide a reliable history, in which case, witnesses may be helpful. The ESC has given a class IIa recommendation to novel diagnostic mechanisms, such as home video recordings.

1.6.2 Orthostatic Hypotension-Induced Syncope

In normal individuals, when blood pools in the venous system (due to gravity) upon standing, cardiac output briefly falls, but quickly returns to normal due to compensatory mechanisms. These mechanisms include increase in heart rate, cardiac contractility, and peripheral vascular resistance. Blood pressure remains little changed

and with cerebral autoregulatory mechanisms, there are no symptoms with changes in position.

Syncope occurs in individuals when these compensatory mechanisms do not occur or are inadequate. Both the ESC and ACC/AHA/HRS guidelines state that two major subcategories of orthostatic hypotension include volume depletion and medication-induced. Common medications include vasodilators, diuretics, and anti-hypertensives, among others. The third subcategory of orthostatic hypotension-induced syncope is neurogenic orthostatic hypotension. For these individuals, the primary pathophysiology involves autonomic failure, and thus, there is lack of compensatory vasoconstriction and increase in heart rate with standing, and there are no other compensatory mechanisms that effectively provide adequate cerebral blood flow. The ACC/AHA/HRS does not differentiate between primary and secondary neurological disease; the ESC does. Primary causes for neurogenic orthostatic hypotension include multiple system atrophy, pure autonomic failure, Parkinson's disease and dementia with Lewy bodies, while secondary causes include diabetes, amyloidosis, spinal cord injuries, and other secondary neuropathies.

1.6.3 Cardiac Syncope

Cardiac syncope is syncope due to cardiac disease. It is not necessarily syncope associated with cardiac disease. The two main causes of cardiac syncope are arrhythmias (bradycardias and tachycardias) or hemodynamic perturbations. Bradycardias (sinus node dysfunction, AV block) and tachycardias (particular ventricular) have the potential to cause syncope by decreasing blood pressure and cardiac output, especially when there is an abrupt change in heart rate one way or the other.

The channelopathies, such as Brugada syndrome, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and arrhythmogenic right ventricular cardiomyopathy are inherited disorders that put patients at particularly high risk for syncope (and potentially sudden cardiac death). Structural heart diseases that cause syncope include left ventricular outflow tract obstructive diseases (aortic stenosis, hypertrophic obstructive cardiomyopathy), acute myocardial ischemia, left ventricular systolic dysfunction, pulmonary embolism, and pericardial tamponade. It is important to keep in mind that in many of these "structural" conditions, the actual cause of syncope is via the Bezold–Jarisch Reflex as discussed earlier with inferior wall myocardial infarction.

Syncope due to various cardiac causes are associated with different risks. For example, complete heart block can cause syncope but is unlikely to cause sudden death whereas ventricular tachycardia is not only likely to cause syncope but also to increase the risk for sudden cardiac death. Thus, classifying patients with cardiac syncope as a high-risk group is not necessarily correct. Also, patients with underlying cardiac disease can experience syncope due to non-cardiac causes. There is also

overlap between the hemodynamic and arrhythmic mechanisms of syncope in patients with structural heart disease. History including lack of prodrome, syncope while in a seated or recumbent position, and family history of sudden cardiac death should prompt consideration of cardiac cause of syncope.

1.6.4 Syncope of Unknown Origin

One thing that neither guideline discusses in any detail is syncope of undetermined etiology. The ACC/AHA/HRS guidelines do mention it and consider unexplained syncope to be when the cause is not determined after an “appropriate” initial evaluation by an “experienced health care provider” (not further defined). This includes an initial evaluation not limited to, but including, a thorough history, physical examination, and electrocardiogram. When considering the history, the ACC/AHA/HRS guidelines clarify that the goal is to identify the prognosis, the cause of syncope (the responsible diagnosis), and other factors, comorbidities and medications that could be contributory. However, unless the episode is witnessed and there is a concomitant measurement of heart rate and blood pressure and perhaps even ECG and EEG recording, it can be difficult to determine precisely what caused TLOC. Neither guideline sheds light on the appropriate next steps for clinicians to take. Often, another episode is required to determine what actually occurred.

1.7 Problems with Classification

There are multiple problems with the syncope classification approach. For example, an abnormality may be seen, such as severe orthostatic hypotension, and may even be present with symptoms of near syncope in a clinical setting; however, this does not necessarily correlate with the cause for syncope at the time it happened. This may appear to be self-evident, but in the clinical setting, causation rather than association alone becomes critical, since many abnormalities are found in patients with syncope and these are not necessarily the cause for the actual episode. A positive tilt-table test, a diagnosis of postural orthostatic tachycardia syndrome (POTS), or identification of an asymptomatic sinus pause are examples that may not explain the syncopal episode. Additionally, syncope is often multifactorial, especially in older individuals.

Another problem with the classification relates to the fact that there is some confusion about risk versus causality. A patient may have risk for sudden death due to a long QT interval syndrome and have a “cardiac cause for syncope” but may pass out from a vasovagal cause. In fact, such a clinical presentation is not uncommon. Additionally, cardiac causes for syncope are not all the same. Cardiac

causes for syncope may actually be “low risk” if syncope is due to a sinus pause or even transient complete heart block. On the other hand, patients with ventricular dysfunction who have risk for ventricular arrhythmias and sudden cardiac death may pass out from some other cause. Therefore, lumping all patients into a cardiac versus non-cardiac cause for syncope does not necessarily separate high from low risk. In fact, patients may be at high risk for death even without a cardiac cause for syncope. Such an example would include a patient who has pulmonary emboli and an ensuing vasovagal episode due to these pulmonary emboli.

Yet another problem is trying to classify patients as cardiovascular and non-cardiovascular syncope. In fact, as has been described, hypoperfusion to (at least) certain areas of the brain is important to cause syncope. Thus, in one sense, all episodes are cardiovascular. Is the vasovagal reflex a cardiovascular cause for syncope, as the mechanisms involved are vasodepression and cardioinhibition? Some may say so, but it is a rather benign cause for syncope and therefore classified differently. Furthermore, a vasovagal episode which may be the cause for syncope, is not necessarily due to a benign cause. Consider that there are multiple reasons to have a vasovagal reflex including specific autonomic triggers such as vomiting and diarrhea, inferior myocardial infarction, aortic stenosis, and other causes which may not necessarily be benign. It is important to recognize that some of the initial models of vasovagal syncope occurred in animals who were bled and then developed bradycardia and hypotension due to sympathetic activation from hypotension.

Despite careful and complete evaluation, part of the classification involves consideration of patients with syncope of undetermined or unknown etiology. This represents a fairly large number of individuals, but the classification is also dependent upon the initial evaluation. Syncope of unknown origin can be simply syncope that has recently occurred, and a complete history, physical evaluation, and ECG was obtained without producing a clear etiology. On the other hand, syncope of unknown origin can be that which involved long-term monitoring and specialty testing such as electrophysiological testing and tilt-table testing, yet the diagnosis remains uncertain. Clearly, future consideration of these dilemmas and the development of a consensus is needed.

1.8 Gaps Remain

Despite the best efforts regarding the understanding of syncope and its mechanisms, causes, and evaluation, in many instances, gaps remain. It is unclear, for example, why transient bradycardia of a few seconds may cause complete loss of consciousness in one individual but have no effect in another. It is uncertain where consciousness arises and what causes it to go away at least for short periods of time. Furthermore, it can be difficult to distinguish different etiologies for TLOC or even determine if loss of consciousness actually occurred, pointing to the fact that we do not completely understand what consciousness is in the first place.

1.9 Conclusion

Syncope is characterized by brief, self-limited cerebral hypoperfusion, and transient loss of consciousness, associated with loss of postural tone, that resolves rapidly and spontaneously. It is a common problem that has many potential causes. All TLOC is not syncope. Unfortunately, the clinical presentations of patients are often not clear. The ESC and ACC/AHA/HRS guidelines define syncope with slight differences and classify syncope in different ways. Both guidelines recognize reflex (neurally-mediated), orthostatic hypotension induced, and cardiac causes for syncope. However, the ACC/AHA/HRS guidelines first classify syncope as cardiac or non-cardiac syncope.

Discovering the underlying cause for syncope in a particular patient may be challenging if the history and physical exam are unrevealing. Risk stratification to distinguish lethal from benign etiologies and to assess risk of recurrence are important in the clinical assessment. The ESC and the ACC/AHA/HRS guidelines both agree that significant gaps in knowledge remain.

Key Points

- Syncope, a symptom, is reflective of multiple diagnoses, mechanisms, and causes.
- Syncope is a self-limited form of transient cerebral hypotension, complete loss of consciousness with associated loss of postural tone and is followed by complete, generally rapid, spontaneous recovery.
- A transient fall of systemic arterial pressure to a level below the minimum needed to sustain cerebral blood flow (i.e., the lower end of the cerebrovascular autoregulatory range) is the most common cause of syncope. Other causes, such as acute hypoxemia, are rare.
- The ESC and the ACC/AHA/HRS guidelines differ regarding definitions and classification.
- The ESCs categorizes syncope into three primary etiologic subsets: reflex (or neurally-mediated), orthostatic, and cardiac (cardiovascular).
- ACC/AHA/HRS emphasize differentiating between cardiac and non-cardiac syncope, before then dividing non-cardiac syncope into reflex (neurally-mediated), orthostatic, and other (rare) causes.
- Syncope of undetermined etiology represents a common problem and is defined differently in the two guidelines.
- Determining the underlying cause for syncope can be challenging, but is of extreme importance, as missing a potentially lethal etiology can be catastrophic.
- Benign causes for syncope often recur and may incur significant morbidity; they represent the majority of episodes for syncope.
- The goal of syncope evaluation is to determine the cause, the chance of recurrence, and the risk of adverse outcomes.

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Chapter 2

The Meaning of ‘Consciousness’ in Syncope and Related Disorders



J. Gert van Dijk

2.1 Different Meanings and Aspects of ‘Consciousness’

This chapter starts with a discussion of ‘consciousness’; first according to dictionary definitions and then in the medical context of impaired consciousness. The underlying neuronal networks will be mentioned briefly. This is followed by a brief discussion of the three normal states of consciousness, i.e. being awake, REM sleep, and non-REM sleep. Abnormal states of consciousness are discussed next, including anaesthesia.

Assessing the level of consciousness relies on responsiveness, motor and memory functions. The various aspects of consciousness will be discussed in the context of ‘Transient Loss of Consciousness’ (TLOC), a diagnostic category designed to aid the differential diagnosis of syncope, as introduced by the European Society of Cardiology in 2001 [1]; the latest version is from 2018 [2, 3].

2.1.1 Dictionary Definitions

Consciousness is hard to define, probably because it represents various overlapping concepts rather than one unitary concept. Wikipedia provides an overview of its many features (<https://en.wikipedia.org/wiki/Consciousness>). Dictionary definitions differ but largely focus on the same aspect: awareness. This example is from the Oxford online dictionary:

The state of being aware of and responsive to one's surroundings
A person's awareness or perception of something
The fact of awareness by the mind of itself and the world

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Awareness in turn is explained as ‘*Knowledge or perception of a situation or fact*’. The first definition could apply to a cat perceiving a mouse or a spider noticing a fly, in which case ‘being aware’ would concern the processing of sensory stimuli at a fairly low level of sophistication. The third definition describes another level entirely, in which the conscious mind is fully ‘self-aware’. In other words, ‘awareness’ can already denote levels of neural integration that range from sensory processing to considering life, the universe, and everything.

The presence of consciousness/awareness is not by itself apparent to a bystander. Making one’s awareness of anything known to someone else requires additional neurological functions, at least motor ones, so a response becomes possible. The first definition above juxtaposes ‘responsive’ as equally important with awareness, which is neurologically untenable. Firstly, awareness can exist without the ability to respond: this happens in states with complete paralysis, e.g. the locked-in state, amyotrophic lateral sclerosis, Guillain–Barré syndrome, and anaesthesia. Secondly, many responses only require processing at a level much lower than is required for self-awareness, such as the Achilles tendon jerk, the corneal reflex, and breathing.

The dictionary defines ‘unconsciousness’ similar to consciousness, but with an added ‘not’: “*Not awake and aware of and responding to one’s environment*”. Note the addition of ‘not awake’, even though ‘awake’ was not mentioned as an element of consciousness. While wakefulness is usually accompanied by awareness, dreams are an obvious example of awareness in sleep.

These examples illustrate that the dictionary definitions assess different aspects of consciousness without necessarily identifying them. The fact that different aspects of consciousness exist, and may co-exist, under the same heading ‘consciousness’ also affects the scientific literature, in which ‘conscious’ can mean ‘not in a coma’, being aware of a sensory stimulus, or being self-aware.

2.1.2 The Medical Context: Content and Arousal

In a medical context, consciousness is classically considered to have two aspects [4], neither of which corresponds directly with awareness:

1. The first, ‘arousal’, describes the level of consciousness as a quantitative scale ranging from fully awake to deep coma. Normally wakefulness and awareness are connected, with awake/aware on the one hand and not awake/not aware on the other, but brain disorders provide exceptions. Someone in a vegetative state looks awake, with spontaneously opened eyes, but betrays no evidence of awareness. Perhaps meditation or the mind blanking for a few moments represents the odd state of being awake but not aware of anything [5, 6].
2. The second aspect is content; it ‘represents the sum of all functions mediated at a cerebral cortical level, including both cognitive and affective responses’ [4]. Note that the limitation to ‘cortical’ may not be correct in view of ‘corticothalamic’ networks. ‘All cortical functions’ imply that ‘content’ comprises language,

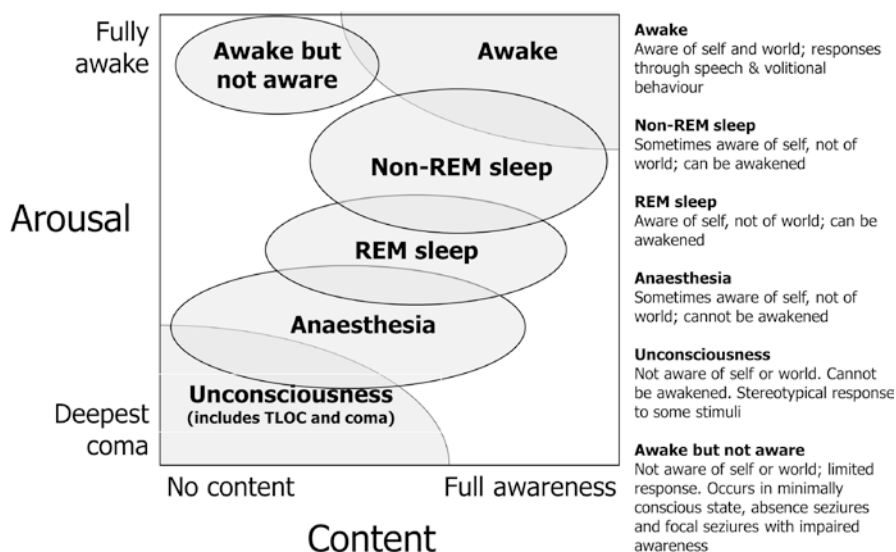


Fig. 2.1 Scheme of consciousness. Various states of consciousness are depicted schematically on two axes, that of content and of arousal. The width, height, and overlap of the various conditions are debatable. The ability to respond is represented in the text, but can be envisaged as a third axis

thought, etc.; awareness belongs in this category and is probably intertwined with many of these functions, from memory to language.

Oddly, ‘unconsciousness’ does not comprise the same two aspects. The noun ‘unconsciousness’ is not normally used to describe that a person is unconscious of a certain fact. Plum and Posner’s textbook makes it clear that ‘unconsciousness’ almost exclusively denotes an impairment of the level of consciousness.

Figure 2.1 shows several states of consciousness on a map defined by both the content and arousal aspects of consciousness.

2.1.3 Normal States of Consciousness

There are three main normal states of consciousness: awake, asleep without dreams (‘non-REM’ sleep), and dream sleep (REM sleep). Awareness may occur in all three states. In the awake state the aware mind is connected with the outside world: not only does information come in through the senses, but it can respond using motor functions.

Waking people up from ‘non-REM’ sleep shows that they were aware of thoughts or perceptions in 23–74% of cases [7]. These perceptions are only reported if people are woken, meaning firstly that the perceptions are only stored in memory for a short while, and secondly that the absence of recollection of awareness of something does not mean there was no awareness.

Awareness is reported by about 80% of people woken from REM sleep [7]. In dreams, the dreamer is self-aware. The dream content is generated while the mind is disconnected from the outside world, but is experienced as real as the information from the outside world that is perceived while awake. While dreams are remembered more readily than the mental activity during non-REM sleep, they still tend to disappear from memory quickly.

Whether blanking of the mind [5, 6] and meditation should be classified as separate normal states of consciousness is dubious. Meditation can cause shifts in EEG content [8] and can be learned, meaning it can be achieved with normal brain circuitry

2.1.4 Abnormal States of Consciousness

Impairments of consciousness can be due to anything causing loss of function of the ascending reticular formation in the brainstem or a sizable portion of the cortex and corticothalamic circuits. The following description of a gradually more severe impairment illustrates that ‘awareness’ by itself is of limited use to assess the level of unconsciousness.

The maximal result to an arousing stimulus is to become fully awake and highly alert, with attention tightly focused on the stimulus. A slight impairment results in less alertness, less attention, and less focused attention. A more severe impairment abolishes the ability to stay awake, resulting in normal sleep under abnormal circumstances. Examples are sleep after vasovagal syncope in children, or after a concussion or tonic-clonic seizure at any age. Once spoken answers are absent, full awareness can no longer be assessed reliably. The word ‘unconsciousness’ is often used once a person can no longer be awoken, and the word ‘coma’ is usually reserved for long-lasting profound impairments. (The unconsciousness in syncope may be much more severe than in many cases of coma, but its short duration means ‘coma’ is not used.) Responses become limited to pain and become limited to stereotypical patterns. The loss of brainstem reflexes, such as corneal and pupillary responses, usually signifies deep unconsciousness; the breathing reflex is often literally the last to be lost.

Two endpoints of severe brain damage deserve mention, because of the involvement of awareness [9]. In the vegetative state, also called the ‘unresponsive wakefulness syndrome’, there are no obvious signs of any awareness, but some automatic functions such as a basic sleep-wake cycle are preserved. Hence, persons in this state can be awake but not aware. In the ‘minimally conscious state’ there is some awareness and processing of external and internal stimuli. Their presence may only come to light using technical means such as functional MRI.

Anaesthesia deserves special mention as a state of abnormal consciousness because it offers insights into the circuitry of consciousness. Anaesthesia normally tries to achieve three goals: the first is to abolish pain, because pain can give rise to unwanted endocrine and neural responses; the second is muscle relaxation, and the third is abolishing awareness of surgical procedures such as being cut [7, 10].

Dreaming occurred in 27% and 28% of patients anaesthetised with propofol and desflurane, respectively [7], showing that awareness need not be completely abolished during anaesthesia. Likewise, responsivity may also be preserved: in the ‘isolated forearm technique’ the blood supply to a forearm is blocked with a cuff before neuromuscular blockade is administered, so patients can still move their hand, should they wish to do so [10]. Note that this does not imply that people later remember any of this. Such responses prove that awareness, both of events in the outside world (‘connected’) and of the mind itself (‘disconnected’), occurs in as many as 37% of normal anaesthesia procedures [7]. Some anaesthetists argue that it is sufficient to aim for ‘no recollection’ of events during anaesthesia, while others prefer to aim for ‘no awareness’ altogether [7]. The latter seems the safer option, as ‘no conscious recollection’ only means there is no explicit memory. Memories can be present implicitly, meaning that they are not available for conscious recollection, but may still have associative consequences [7].

Various anaesthetic drugs provide means to understand how awareness is normally controlled [10]. For instance, ketamine may give rise to awareness in the form of disconnected consciousness with hallucinations and distorted self-perceptions [10].

2.1.5 Networks of Arousal and Awareness

No-one yet understands the ‘mind-body problem’, i.e. how neuronal circuits allow self-awareness. What was once the domain of philosophers is now a subject of neuroscience. Insight into how the brain organises complex tasks is growing thanks to a variety of techniques [9, 11]. These techniques measure ‘functional connectivity’ between brain areas. Widely used techniques are functional magnetic resonance imaging (fMRI), magneto-encephalography (MEG), and electro-encephalography (EEG), each with advantages and disadvantages. For instance, fMRI has good spatial resolution; MEG and EEG have excellent temporal resolution and EEG is cheap and highly adaptable. They measure regional activity such as changes in blood flow (fMRI) or electrical synaptic neuronal activity (EEG). A correlation of activity between brain areas indicates functional connectivity. Such ‘networks’ can be investigated while subjects are at rest or during specific tasks [9].

On a basic level arousal relies on the ascending reticular activating system and the reticular formation. Above that level thalamic and thalamocortical circuits play a major role [12]. The content part of consciousness is said to depend more strongly on corticocortical connectivity.

As said, content and arousal are strongly linked, in that full awareness occurs preferentially during the awake state. The strong link between content and arousal suggests that they share a crucial part of their circuitry. It has been suggested that the layer 5 pyramidal cortical neurons represent the linking pin [12]. This theory predicts that it is impossible to become aware of any processing that does not pass this layer. The brain indeed performs many complex tasks of which we cannot become aware of how they are carried out; we merely learn the result. Examples are

how the basal ganglia or cerebellum compute movements, or how the brain constructs sentences [12]. It may also be impossible to become aware of how we become self-aware.

While it is not known how the brain generates the mind, the search is on for the ‘neural correlate of consciousness’ (NCC). This describes the neuronal network or activity that allows awareness to exist [13, 14]. Even though the real NCC has not been isolated, some of its probable characteristics have been identified [14].

Opinions diverge on the site of awareness: [15] some propose a focal site that is involved with processing of sensory changes or pathways dealing with the ensuing perceptions; others point to fronto-parietal attention networks, and some look for global brain activity. Awareness can be investigated by offering subtle sensory stimuli, some of which are noticed consciously while others escape detection. Comparing the two conditions reveals which areas function during awareness of the stimulus. One such study showed an increase in connectivity between ‘modules’, arguing for awareness to take place on a global brain level [15].

2.2 Consciousness in the Medical Context of TLOC

The description of consciousness impairments earlier showed that the level of consciousness is represented in awareness, attention, alertness, spontaneous behaviour, speech, and in responses to visual input, speech, touch, and pain, that together involve a large portion of the entire brain.

Still, awareness can be impaired by focal brain dysfunction. In ‘absence seizures’ and ‘focal seizures with impaired awareness’, previously called complex partial seizures, patients stand or sit upright but otherwise undertake no actions. They respond little to speech or touch and later usually have amnesia for the spells. In these spells self-awareness is affected, but motor control remains intact. How a focal dysfunction can cause an impairment pointing to a global brain problem will be explained later. As said, the term ‘unconsciousness’ is almost never used for such spells. It is instead used for severe impairments of the arousal aspect of consciousness, and these are invariably due to widespread loss of function of at least the cerebral cortex, involving most or all cortical functions, i.e. sensory, motor, and cognitive ones. Hence, ‘unconsciousness’ usually indicates the loss of a collection of functions rather than the isolated loss of one specific brain function, even if the word itself, taken literally, suggests otherwise. Examples of disorders causing this ‘complete unconsciousness’ are concussions, intoxications, hypoglycaemia, tonic-clonic seizures, and syncope. These all cause dysfunction of much of the cortex, albeit in different ways. Hence, they result in a similar set of signs and symptoms. While self-awareness is one of them, it can only be assessed using other functions, not directly. For practical purposes such as diagnosis it is easier to focus on these other functions.

From here on, a distinction must be made between patients in whom a neurological examination can be performed and those in whom the impairment of

consciousness has resolved before they are seen by a doctor. The discussion will focus on the latter situation, of which syncope is a prime example. In such patients, the diagnosis of impaired consciousness must rest on information from history taking. Three features then indicate ‘loss of consciousness’ (LOC): amnesia, falling (and other indications of abnormal motor control), and unresponsiveness. Adding a short duration then creates the diagnostic category ‘Transient Loss of Consciousness’ (TLOC).

Any condition fulfilling these criteria will be labelled TLOC, and this also holds for psychogenic TLOC. While such patients exhibit the outward appearance of LOC to the untrained eye, ictal EEG recordings and observation by trained observers reveal that cortical function is largely intact. The TLOC criteria cannot discriminate between the gross cerebral dysfunction of syncope or tonic-clonic seizures and the much subtler psychological dysfunction of psychogenic TLOC. This is why the phrase ‘apparent LOC’ was used in the European definition of TLOC.

2.2.1 Differences between the European and North American Guidelines

‘Transient Loss of Consciousness’ bundles disorders that share enough clinical characteristics to feature in one another’s differential diagnosis. It was defined in the latest guidelines on syncope of the European Society of Cardiology as follows: [2].

TLOC is defined as a state of real or apparent LOC with loss of awareness, characterized by amnesia for the period of unconsciousness, abnormal motor control, loss of responsiveness, and a short duration.

Note that LOC relies on three characteristics, and that adding ‘short duration’ creates the subset TLOC. TLOC comprises three main groups: syncope, tonic-clonic seizures, and psychogenic TLOC. The short duration excludes metabolic and toxic causes, as the difference in duration is long enough to prevent confusion. The ACC/AHA/HRS guidelines from North America [16] contain some differences. Loss of consciousness and TLOC were defined as follows:

Loss of consciousness (LOC):

A cognitive state in which one lacks awareness of oneself and one’s situation, with an inability to respond to stimuli.

TLOC:

“Self-limited loss of consciousness can be divided into syncope and nonsyncope conditions. Nonsyncope conditions include but are not limited to seizures, hypoglycemia, metabolic conditions, drug or alcohol intoxication, and concussion due to head trauma.”

There are several differences between the two sets of guidelines. The North American definition of LOC limits consciousness to one content aspect and one arousal aspect. The groups of disorders constituting TLOC are divided into syncope

and non-syncope, although epileptic seizures and psychogenic spells differ as much from one another as they do from syncope. More importantly, TLOC represents a much wider set of conditions than the original European definition, in that metabolic conditions and intoxications are included even though they last much longer, and no distinction is made between types of epileptic seizures, including types without falling.

2.2.2 The Four Defining Features of TLOC

The ESC definition mentioned four elements that can be used in daily practice to check whether TLOC was present [3, 17].

1. The first is amnesia for the period of LOC, apparent as a gap in memory. A typical experience is people finding themselves on the floor without recollection of a fall.
2. ‘Abnormal motor control’ concerns one universal feature and several variable ones. The invariable feature is a tendency to fall. The variable features are abnormal postures, such as flexion or extension of the arms; myoclonic jerks or no movements, stiffness or flaccidity; the eyes can be open or closed; a tongue bite or not; abnormal sounds or not, incontinent or not.
3. The loss of responsiveness consists of no response to touch or speech.
4. To be short the duration of LOC should be less than 5 min; this accommodates the usually overly long estimates of eye witnesses.

All four aspects have to be present to qualify an event as TLOC [3]. Figure 2.2 shows which disorders may be considered when one criterion is absent. The criterion ‘abnormal motor control/falling’ means that disorders in which patients remain actively upright are not TLOC: these are ‘absence seizures’ and ‘focal seizures with altered awareness’ (formerly known as ‘complex focal/partial seizures’).

2.3 Specific Disorders Causing LOC

2.3.1 LOC in the Distinction between Syncope and TIA

Syncope is TLOC due to cerebral hypoperfusion, so it is a neurological symptom due to a cardiovascular cause. Although this also holds for transient ischaemic attacks (TIA’s) and stroke, the hypoperfusion in syncope concerns the entire brain and is due to a systemic circulatory problem, while in TIA and stroke the disturbance affects part of the brain and is due to a local vascular problem. The distinction can be simplified as follows: a TIA is a focal neurological deficit without LOC, whereas syncope is LOC without focal deficits [1]. As the details can be more

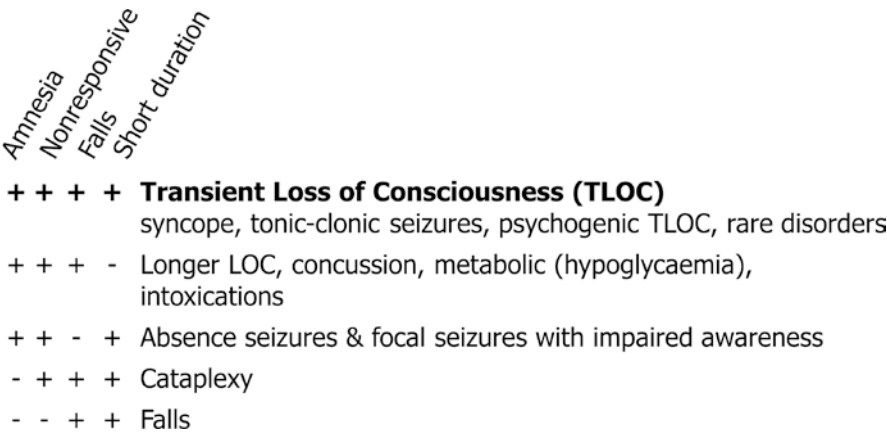


Fig. 2.2 Elements of Transient Loss of Consciousness (TLOC). To be considered TLOC, a period of apparent loss of consciousness must fulfil four criteria: amnesia, abnormal responses to touch or speech, falls and other indications of abnormal motor control, and a short duration. These features indirectly point to a loss of self-awareness and show that the episode concerned a major loss of cerebral function, not limited to awareness. A short duration sets TLOC apart from other conditions causing full loss of consciousness. If all TLOC conditions but falling are fulfilled, there cannot have been a global cerebral dysfunction; two types of epilepsy can cause a selective loss of awareness. Cataplexy occurs as a paralysis with intact consciousness; it is rare and occurs most often in the context of the sleep disease narcolepsy. Falls that are not due to loss of consciousness are not accompanied by amnesia or a loss of responses

complex, two questions can be asked: are there focal signs and symptoms in syncope, and can LOC be due to focal cerebral ischaemia?

2.3.2 Focal Signs in Syncope

Head turning, eye deviation, and asymmetrical limb movements and postures are common in tilt-induced syncope [18, 19]. These features may suggest a focal nature, but usually are not likely to be noticed in daily practice, as they last only 10–20 s. and occur just after someone will have fallen, in the presence of an unprepared and often distraught observer. Even when such signs are noted, they differ from similar symptoms in other conditions: for instance, eye deviation in TIA and epilepsy concerns a sustained and systematic deviation to one side. Myoclonic jerks and postures in syncope are often asynchronous and may differ in amplitude between sides [18, 19], but are not systematically restricted to one side. Such features are ascribed to disinhibition [18, 19], and their asymmetry suggests that local variability governs the details of their occurrence.

Focal neurological deficits were reported in 37 (5.7%) of 540 subjects investigated for syncope (*n* = 401) or presyncope (*n* = 139), lasting a median of 15 min

[20]. This high rate has not been confirmed and is contradicted by experience with tilt table testing. A bias related to either the presence of focal features or of LOC cannot be excluded. The criteria by which LOC was established were not described; using the specified TLOC features may improve the reliability of assessing TLOC. Moreover, syncope can probably be assessed more confidently than presyncope, in which LOC does not occur.

2.3.3 *LOC in TIA and Stroke*

Syncope or presyncope was reported to occur in 4.9% of 772 subjects presenting with stroke or TIA, without major obstruction of the cerebral arteries [21]. As there appear to be no other reports of LOC occurring during TIA or stroke in the territory of the carotid arteries, an unidentified reporting bias again seems likely.

LOC can be the result of thalamic damage or massive loss of function of both hemispheres, so LOC might occur in a carotid artery TIA if there is obstruction of several cranial arteries, or in combination with orthostatic hypotension. Orthostatic TIAs are well-known. Although TIAs are commonly due to emboli, about 6% of TIAs occur during circumstances suggesting low blood pressure [22]. However, LOC has not been described in this context. This also holds for ‘limb shaking TIAs’, in which there is rhythmic shaking of an arm or a leg, but not of the face. Limb shaking TIAs occur in patients with obstruction of one internal carotid artery and little cerebral reserve capacity during events associated with low blood pressure [22].

TIA’s and LOC can occur together in vertebrobasilar TIA’s and probably also in the subclavian steal syndrome. LOC is then due to focal ischaemia of the brainstem that also causes signs clearly pointing to the posterior cerebral circulation, such as diplopia, dysarthria, paresis, or ataxia. Observed LOC was noted in only 3% of 407 cases with a vertebrobasilar TIA or stroke [23]. Less severe impairments of consciousness, such as somnolence or stupor, occurred mostly in the distal vertebrobasilar artery territory, such as in the ‘top of the basilar syndrome’. [23, 24] Consciousness is never impaired as the sole expression of vertebrobasilar disease. [24] This, as well as the long duration of symptoms and signs in TIA’s, means that a vertebrobasilar TIA need not feature in the differential diagnosis of LOC without focal neurological signs or symptoms.

2.3.4 *LOC in Syncope*

Impairments of consciousness in syncope are related to the level and rate of cerebral hypoperfusion. As the cortex is most susceptible to ischaemia, the first functions to be lost are those of the content aspect depending on corticocortical connectivity. The most complex functions are usually affected the most [25]: Attention,

concentration, and presumably self-awareness and memory storage. As hypoperfusion continues or deepens, the arousal aspect is affected and consciousness is lost.

Symptoms also least likely to be noticed when neuronal dysfunction develops fast. In arrhythmic syncope with sudden asystole, the first awareness of anything amiss may well be coming round after the fact. Reflex syncope provides more time to notice symptoms. In an experimental study on sudden syncope, patients' eyes stopped moving and they could no longer act voluntarily, although their later recollection of this proved that they were still aware. [26] People hardly ever recall falling in reflex syncope, suggesting that the imprinting of memories stops just before motor control is lost.

Low blood pressure can occur for long periods in neurogenic orthostatic hypotension (nOH). A loss of concentration was noticed in nOH due to Parkinson's disease. [27] If blood pressure decreases a bit more in nOH, awareness may become too impaired to take decisions such as to sit down, but not impaired enough to fall. This 'inability to act' may last minutes to hours, and can be mistaken for sleepiness or a motor disorder.

After syncope, a minority of patients report perceptions during LOC, similar to 'near death experiences'. [28] Near death experiences occur in anaesthesia, cardiac arrests, syncope, and meditation, [29] and are therefore not linked to dying at all. The intensity of the experience proved to be related to fantasy proneness [30] and to the level of detail. [29] The apparent rarity of reports of these experiences in syncope does not prove that dream-like experiences seldomly occur during syncope; it is possible that they occur more often but are usually not stored in memory, much like the awareness during non-REM sleep and anaesthesia.

As the loss of function in syncope continues, signs emerge that are linked to the depth of hypoperfusion. Flattening of the EEG represents a complete loss of cortical function in syncope. [18] Signs associated with EEG flattening likely concern brainstem activity: making sounds, snoring, upward deviation of the eyes, roving eye movements, and tonic posturing of the arms. [18, 19]

2.3.5 *LOC in Epilepsy*

Epilepsy may be generalised, meaning it affects the entire cortex, or focal, meaning only a portion of the cortex is affected. In either case the connectivity between brain areas means that the excess activity in a seizure does not need to be limited to the area in which the seizure originates. In fact, activity in some areas other than the primary seizure area may well be less than normal, so some expressions of epilepsy represent reduced function.

In some seizures, consciousness is completely unaffected, meaning patients may notice an abnormal sensation or abnormal movements of a body part with full attention. If consciousness is affected in epilepsy, this is more diverse than in syncope. [25] Three types of epilepsy show important impairments of consciousness:

1. The first are absence seizures, in which children stop what they are doing and may continue some automatic tasks, but do not fall (these seizures are not TLOC). The EEG shows spike-wave complexes over the entire head, making this a generalised seizure. Even so, not all cortical functions are affected (there are, for instance, no gross movements suggesting the primary motor cortex is dysfunctional). The maximum amplitude of the spike-wave complexes over frontal regions shows that absence seizures affect some areas more than others. Combined EEG and fMRI studies showed increases in the thalamus and decreases in various cortical areas. [25] In a study comparing absence seizures with more or less impaired behavioural responses, there was more brain activity when responsiveness was more compromised than when it was not. [31] The authors proposed that the impairment of consciousness was due to global rather than focal disturbances.
2. Focal seizures with abnormal awareness are the second type of epilepsy with altered consciousness. Clinically the seizures resemble absence seizures, with patients no longer responding, continuing some automatic tasks such as sitting or standing (these seizures are not TLOC either), with later amnesia. Such attacks commonly originate in the temporal lobe. [25] When consciousness is impaired, the seizure has often spread to the contralateral temporal lobe. There is reduced blood flow in the upper brainstem, medial thalamus, and hypothalamus during these seizures, [25] suggesting decreased neuronal activity. An EEG connectivity study in such seizures showed that there was an increased degree of EEG synchronisation between the thalamus and parietal cortex, areas involved in awareness. [32] Note that a precise degree of connectivity appears to be crucial for many functions. While too little synchronisation may well characterise lowered states of consciousness, it is not true that more synchrony always means better function. The authors suggested that the excessive synchronisation overloaded structures involved in conscious processing. [32]
3. The third type of epilepsy in which consciousness is impaired concerns tonic-clonic seizures. These may start with a focal seizure followed by a spread of excessive activity or as a primary generalised seizure. In either case there is strong tonic muscle activation of the entire body with complete loss of all normal motor function. A lateral tongue bite may happen here. Patients fall, so these seizures are TLOC. The tonic activity is due to excessive cortical electrical activity. Current theories propose that the excessive activity is actively suppressed, [33] first for very short periods, and then for longer ones. The alternating overactivity and suppression turn the tonic phase into the clonic phase, with repetitive myoclonic jerks. As the suppression intervals increase, the jerks become lower in frequency but larger in amplitude. The last clonic movements herald the stop of excessive EEG activity. However, the suppression continues for a while, giving rise to a deeply impaired postictal consciousness. This is followed by abnormal sleep, from which patients cannot be easily wakened. Once awake, higher cortical functions take time to recover, causing the imprinting problem and confusion that help to differentiate these seizures from syncope.

The pathophysiology of LOC in tonic-clonic seizures has been investigated less frequently than in other epilepsy types, because movement artefacts obscure subtle EEG alterations, and safety reasons preclude MRI studies during such seizures. [25] SPECT studies allow the possibility to inject a tracer during a seizure and study the places where it was retained later. Such studies showed increased activity in some brain areas and decreases in others. [25] Of interest, the cerebellum showed increased activity in late ictal and postictal periods. These might be the origin of the suppression that ends the seizure and causes the postictal LOC. [25]

2.3.6 LOC in Psychogenic TLOC

It is difficult to assess the nature of the impairment of consciousness in psychogenic nonepileptic seizures (PNES) or psychogenic pseudosyncope (PPS). PNES and PPS probably represent the same psychiatric disorder, and they are distinguished only because they are seen by different specialists. [34] The EEG is normal during PNES and PPS, showing that there is no overall gross brain dysfunction as in syncope. Likewise, purposeful movements during spells of which patients later remember nothing show that many brain functions continue normally. [35] Although some patients with PNES or PPS report a complete absence of any awareness during the spells, many patients state that they were partially aware of their surroundings, but had limited ability to respond. [35] In psychiatry such disparate impairment is described as 'dissociation', meaning that the usually integrated functions of awareness, memory, and perception of the environment are disrupted. Whether these functions can indeed become wholly independent is unknown, as is the neural substrate of dissociation. [35] The lack of evidence of a neuronal mechanism should not be used as evidence in favour of the concept that patients have volitional control over their attacks, [36] as they perceive no such control and stating otherwise may be damaging.

2.4 Conclusions

The word 'consciousness' is used in different ways, so clarity may be improved by stating which function is meant. 'Self-awareness' is an important part of the 'content' aspect of the broad concept 'consciousness'. Its neural correlate has not been identified yet. More is known about the circuitry of the 'arousal' aspect that describes impaired levels of consciousness, ranging from awake to deep coma.

While the content and arousal aspects are linked, awareness can be present in situations with a lowered arousal level, such as sleep and anaesthesia. These examples also prove that the various aspects of the broad concept 'consciousness' can function at different efficiency. Absence seizures and focal seizures with impaired awareness are examples of differential impairment, in which self-awareness is

affected but motor control remains intact; both are due to a focal cortical disturbance with widespread cerebral consequences.

If the impairment affects much larger areas of the brain, ‘unconsciousness’ does not and probably cannot concern an isolated loss of ‘self-awareness’; the latter then is only one part of a much more widespread impairment, involving loss of sensory, motor, and cognitive functions. Concussions, intoxications, hypoglycaemia, tonic-clonic seizures, and syncope all cause such widespread loss of function of at least the cerebral cortex, albeit in different ways. Hence, they all result in a very similar set of signs and symptoms, of which three are readily available to aid diagnosis: the combination of amnesia, falling (plus other indications of abnormal motor control), and unresponsiveness indicates ‘Loss of Consciousness’ (LOC). Adding a short duration creates the category ‘Transient Loss of Consciousness’ (TLOC), useful to limit the differential diagnosis.

Conflict of Interest The author declares no conflicts of interest.

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Chapter 3

Prognosis of Syncope Across the Diagnostic Spectrum



Steve W. Parry

3.1 Introduction

Transient loss of consciousness (TLOC) covers a disease spectrum that embraces conditions from pulmonary embolism to subarachnoid haemorrhage, trauma to hypoglycaemia, and seizures to syncope. Accordingly, prognostication across the spectrum of TLOC is a dark art reliant on the underlying disorder, with outcomes from immediate and full recovery to disability and death possible, contingent upon the proximate cause of the TLOC. Syncope, the commonest cause of TLOC with outcomes ranging from the benign to the ultimately sinister depending on the pathophysiology underlying the consciousness disturbance, will be discussed in this chapter.

3.2 What Is Prognosis in the Context of Syncope?

Prognosis is defined in the Cambridge English Dictionary as “a doctor’s judgment of the likely or expected development of a disease, or of the chances of getting better” (<https://dictionary.cambridge.org/>). As we shall see, the doctor’s judgement can be an important step on the road to estimating prognosis, but this judgement needs the bricks and mortar of clinical evaluation and judicious diagnostic testing to complete the diagnostic process that informs it. In addition, while the bedrock of the scientific literature specific to syncope prognosis focuses primarily on mortality, recurrence prognosis is also crucial given its impact on ability to drive, work, live independently and avoid both physical and psychological injury. Arguably these

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carry nearly as important a weight as mortality and deserve the same attention from researchers investigating prognosis in syncope.

While the symptom of syncope is relatively easily defined, causation can be much more difficult to establish, not infrequently making prognosis more difficult to assess. However, that likely “expected development” is of paramount importance to patients and those treating them given the potential for adverse outcomes from recurrent symptoms to death. In this chapter I will discuss prognosis in terms of what is important to patients, namely the likelihood of symptom recurrence and mortality over different time frames (short and long term) following the initial presentation. In doing so I will discuss the tools of the trade that can inform prognostication alongside the clinical features that help the clinician provide meaningful advice to his or her patient. First, however, it is important to examine the determinants of prognosis in syncope.

3.3 Determinants of Prognosis in Syncope

The importance of the “expected development” of syncope is that for a small but significant number of those affected, the ultimate poor outcome, death, is a possibility. In various populations studied the risk of death is predominantly related to whether there is an underlying cardiac cause for the syncope. In the Framingham Heart Study, 822 of 7814 participants in the general population studied had syncope over 17 years follow-up, with cardiovascular disease and cardiac syncope significantly associated with mortality (hazard ratio 2.01, 95% confidence interval [CI] 1.48–2.73) [1]. No such association was seen with vasovagal syncope (VVS) [1]. In a primary care population, 12% of 2785 patients with syncope had a serious outcome at 1 year with cardiovascular risk factors and comorbidity and age being the main predictors [2]. Kapoor’s study of 433 hospitalised patients found a 51% five-year mortality in those with a cardiac cause versus 24% in those with non-cardiac or unknown cause [3], while a variety of Emergency Department (ED)-based studies have similarly shown that cardiac disease per se, as well as cardiac syncope, are strong predictors of mortality [4]. Indeed, much of the literature over the last decade or so on prognosis and its sister, risk stratification, has been derived from ED data, with a recent position statement providing a sensible overview of high- and low-risk factors for poor outcomes (Table 3.1) [5]. However, there is inadequate focus on two further key contributors to prognosis, namely prior syncope and orthostatic hypotension (OH).

In a large registry-based study, Ruwald and colleagues studied 37,017 first hospital admissions with syncope compared to 185,085 non-syncopal controls [6]. All-cause mortality was significantly higher in those with syncope (8.2% versus 7.1%; HR 1.06; 95% CI 1.02–1.10), as was recurrent syncope, cardiac event hospitalisation, stroke, and cardiac device implantation [6]. While the authors’ suggestion that the syncopal episode may be a marker of underlying cardiac disease may be a

Table 3.1 High- and low-risk factors

Low-risk factors	High-risk factors
<i>Characteristics of the patients</i>	
Young age (<40 years)	Older age and structural heart disease
<i>Characteristics of syncope</i>	
Only while in standing position	During exertion
Standing from supine/sitting position	In supine position
Nausea/vomiting before syncope	New onset of chest discomfort
Feeling of warmth before syncope, or feeling “hot” or “cold”	Palpitations before syncope (although may occur with reflex faints)
Triggered by painful/emotionally distressing stimulus	
Triggered by cough/defaecation/micturition	
<i>Factors present in the history of the patient</i>	
Prolonged history (years) of syncope with the same characteristics of the current episode	Family history of sudden death
	Congestive heart failure
	Aortic stenosis
	Left ventricular outflow tract disease
	Dilated cardiomyopathy
	Hypertrophic cardiomyopathy
	Channelopathy including arrhythmogenic right ventricular cardiomyopathy
	Left ventricular ejection fraction <35%
	Previously documented arrhythmia (ventricular)
	Coronary artery disease
	Congenital heart disease
	Previous myocardial infarction
	Pulmonary hypertension
	Previous ICD implantation
<i>Symptoms, signs, or variables associated with the syncopal episode</i>	
	Anaemia (Hb <9 g/dL)
	Lowest systolic blood pressure in the ED <90 mmHg
	Sinus bradycardia (<40 bpm)
<i>ECG/features^a</i>	
	New (or previously unknown) left bundle branch block
	Bifascicular block + first degree AV block
	Brugada ECG pattern
	ECG changes consistent with acute ischemia

(continued)

Table 3.1 (continued)

Low-risk factors	High-risk factors
	Non-sinus rhythm (new)
	Bifascicular block
	Prolonged QTc (>450 ms)

According to characteristics of the patient and the syncopal episode, the subject can be defined as low, high, or indeterminate risk. Low risk: patients with one or more low-risk characteristics and without any high-risk characteristics. High risk: patients with at least one high-risk characteristic. Intermediate or indeterminate risk: Patients without any high- or low-risk characteristics, or patients with only low-risk factors and some comorbidities such as chronic renal failure, respiratory failure, hepatic failure, neoplasm, cerebrovascular disease, or previous history of heart disease. Note that finding any of these abnormalities does not always lead to a definite diagnosis
ICD Implantable cardioverter defibrillator, *AV* atrioventricular

From Costatino et al. [5]

^aNote that not all the ECG patterns are covered by the table and some other ECG patterns could be considered in stratifying the patients risk such as short QT syndrome, early repolarisation, ECG findings indicating hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and incidental finding of Q wave

reasonable one, there are insufficient data to support it, and the limitations of a post-hoc registry study are evident, substantial participant numbers notwithstanding.

Orthostatic hypotension (OH) has long been associated with morbidity and mortality in syncope, with the assumption made that the association was related to age, frailty, and comorbid conditions rather than OH as a primary causal factor. Recent work from the Malmo Diet and Cancer Study population expands on previous work demonstrating poor cardiovascular outcomes in association with OH [7]. Of the 30,528 middle-aged (mean 58 ± 8 years) participants followed prospectively, 524 (1.7%) were hospitalised for unexplained syncope, and 504 for OH (1.2%). Both were predictive of all-cause mortality, heart failure, and atrial fibrillation, with syncope associated with aortic stenosis and OH with stroke in addition. OH was also particularly associated with comorbid diabetes, though the degree of overlap between OH and syncope was not specified [7]. However, in tandem with a growing body of evidence on the links between OH, cardiovascular disease and mortality [8], it is clear that further work is needed to disentangle association from causation.

In the hunt for a risk stratification tool with a clinically appropriate sensitivity and specificity profile, researchers in the ED have uncovered a number of other risk factors. The most prominent are the cardiac biomarkers: high sensitivity troponins T and I (hscTnT/I), brain natriuretic peptide (BNP), and N-Terminal-proBNP. All four were evaluated in one study of 1538 ED attendees with syncope examining diagnostic accuracy for cardiac syncope and prognostic accuracy for death and major adverse cardiac events (MACE) [9]. Diagnostic accuracy was higher than the EGSYS (Evaluation of Guidelines in SYncope Score) [10] comparator chosen for the study for all four biomarkers (area under the curve (AUC), 0.77–0.78 [95% CI 0.74–0.81; *p* < 0.001]), while mortality and MACE were predicted more successfully by the biomarkers than three of the four syncope rules assessed, the exception being the Canadian Syncope Risk Score (CSRS) [11]. In a similar study in 3392 individuals with syncope across 11 EDs in the USA, hsc TnT and NT-proBNP

predicted short-term mortality and serious cardiac events [12]. Gibson and colleagues meta-analysis of 17 relevant studies broadly agreed with the items discussed so far, with the addition of blood urea nitrogen (positive likelihood ratio 2.86, 95% CI 1.15–5.42), while younger age was predictive of lower risk. Symptoms around the time of syncope did not alter risk, though dyspnoea had significant positive and negative likelihood ratios [13].

Thus, while it is clinically sensible to follow the guidance of the ED consensus group guidance (Table 3.1) [5] in assessing the factors that determine prognosis in syncope it seems prudent to also take account of prior syncope, OH status, and cardiac biomarkers. Many of these factors help with the process of prognostication of mortality and other serious outcomes, but the determinants of recurrence are more difficult to ascertain, despite the fact that recurrence can be of huge significance to individual sufferers. Recurrence of apparently clinically benign conditions like vasovagal syncope can have important implications for quality of life, driving, occupation, and some leisure activities and is complicated in some patients by the difficulties of discerning “real” events from dissociative syncopal symptoms. In one of the Danish registry studies, the key determinants of syncope recurrence in older adults (age 50 years and over and split by under and over 85 years cut off groups) were in essence increasing age, cardiovascular risk factors, and drugs affecting blood pressure [14]. The last two disproportionately affected older rather than the 50–85-year-old patients [14]. Others note that syncope frequency, palpitations pre-collapse, and presence of a prodrome presage syncope recurrence [15], while frequency of events in the year prior to presentation is more predictive in neurally mediated syncope [16].

3.4 Short-Term Prognosis in Syncope

Studies on short-term prognosis in syncope tend to be sited in EDs and associated with the development and validation of risk stratification tools. These utilise a combination of many of the determinants of poor prognosis discussed above but have yet to gain widespread traction in day to day clinical practice [17]. The tools, often in the form of a decision rule, tend to underestimate risk, particularly in older patients, and focus on hard syncope related binary yes-no factors rather than those less easily quantifiable risks including recurrence or injury and the need for urgent treatment of an underlying cause of syncope. These are arguably nearly as important as mortality from a risk stratification perspective of the patient’s entire syncope experience. Importantly, there is little current evidence that the most studied rules to date (Osservatorio Epidemiologico sulla Sincope del Lazio [OESIL], San Francisco Syncope Rule [SFSR], and EGSYS) provide any improvement on clinician judgement in predicting short-term serious outcomes [18]. However, the studies have yielded a wealth of useful information on short-term prognosis. In their systematic review of syncope mortality and recurrence, Solbiati et al. examined 25 studies in the ED, 15 of which were syncope rule development and/or validation studies, and found that short-term mortality was <1% at 10 days, <1.6% at 30 days but with

major adverse events in 7% and 11%, respectively [4]. The 10-day composite death and major event outcome was 9% [4]. A Canadian study of 51,831 patients with syncope who were discharged from the ED found a 30-day mortality rate of 0.4% and for those admitted of 1.2%, with considerably lower costs per patient for those sent home [19]. Again, these data suffer from well-rehearsed issues surrounding uncontrolled registry studies. More recently, Thiruganasambandamoorthy et al. [20] found that 7.5% of 5581 attendees at six Canadian EDs had serious outcomes, 207 of which were arrhythmic. Usefully, electrocardiographic monitoring identified serious arrhythmias in the majority of patients within 6 h of presentation, and 91.7% within 15 days. CSRS scores were assessed, with low-risk patients' serious arrhythmias identified within 2 h, and medium- to high-risk patients within 6 h. There were no ventricular tachyarrhythmias or sudden cardiac death in low-risk patients versus 6.3% of high-risk patients [20]. Though clearly further work is needed to replicate these findings with real-world application data, they offer a promising bridge between clinical utility and risk stratification scoring tools while providing insight into cardiac arrhythmic prognosis in ED attendees with syncope.

3.5 Long-Term Prognosis

While short-term prognosis is relatively easy to define and measure with reasonable confidence and consensus [21], long-term prognosis is less clear cut. First the definition of long-term varies, with many studies reporting one-year outcomes but arguably the years after that are equally as important to individual patients, their clinicians, and the health care systems caring for them. However, it then becomes more difficult to disentangle adverse outcomes related to the index syncopal event rather than additive comorbidities, evolution of the conditions contributing to syncope, the medications and interventions used to treat them, and the ageing process per se. Solbiati et al's systematic review found a variable mortality rate of between 5.7% and 15.5% at 1 year with a pooled estimate of 8.4% (95% CI 6.7–10.2%), with mean ages of the nine studies considered ranging between 41 and 74 years [4]. A more current systematic review of 19 studies reflecting up to 4.2 years follow-up of 98,211 patients found similar one-year pooled mortality in the 12 relevant studies examined of 7.0%, with device implantation in 6% [22]. The majority of these were in the first 30 days, echoing the early arrhythmia detection noted by Thiruganasambandamoorthy et al. previously [20]. However, mortality rose steeply over subsequent longer-term follow-up in two of the studies reporting it, with 4.9% mortality at 30 months but 21% at 4.2 years follow-up [22, 23]. This last study [23], the only one reporting follow-up so far removed from the index syncopal event [22], was part of the Danish population registry series of studies on syncope from Ruwald and colleagues, again with some of the potential confounding issues already discussed. The size of the population, 37,705 individuals with syncope, mitigates these somewhat, and given the association with increasing age, heart failure, and CHADS₂ score in these individuals [23] the findings are perhaps less surprising

than at first glance. Regardless, these ED attendees had a significant mortality burden at 1 year, with a considerable increase over successive years.

3.6 Syncope Recurrence

In Solbiati et al's systematic review of 25 studies involving 11,158 patients, recurrence rates increased in a near-linear manner over time from 0.3% at 30 days to 22% at 2 years follow-up, as they noted, consistent with a further Danish registry study's findings [14]. Leafloor and colleagues' further more extensive systematic review found 16% recurrence in two of the 19 included studies reporting it, though these studies reported on only 399 of the 98,211 patients in the full review [22].

3.7 New Developments in Syncope Prognosis?

The search for a more informative syncope risk score continues apace, with work continuing on both honing previous tools and the development of new ones. One particularly promising recent study in older individuals, the FAINT score, had high sensitivity (96.7%, 95% CI 92.9–98.8%) though low specificity (22%, 95% CI 20.7–23.8%) in predicting 30-day mortality or serious cardiac outcome, and proved better than physician judgement in assessing risk (AUC 0.704; 95% CI 0.669–0.739) [24]. The FAINT score was derived from Bayesian statistical techniques with history of arrhythmia, heart failure, initial abnormal ECG, raised pro-BNP or hsc TnT providing its backdrop. Given the existing literature these are intuitively likely to provide useful clinical information, but further validation is needed before widespread adoption. An alternative approach was taken by Duckheim et al. who examined the utility of deceleration capacity (DC), a powerful predictor of outcomes following myocardial infarction and in heart failure. DC was compared with the SFSR in 395 syncopal patients attending the ED with the main outcome being mortality at 80 days. DC was significantly lower in those who died (AUC 0.85; 95% CI 0.71–0.98), while the SFSR failed to predict death in four of the eight who died, raising the possibility of use of DC to assess low-risk patients in the ED setting [24]. Further refinement of such tools is vital if we are to predict our patients' syncope trajectories with any degree of accuracy.

3.8 Prognostication in Syncope: Dark Art or Science?

The art of prognostication in syncope has improved considerably in the last decade or so as attempts to provide (particularly) ED clinicians with the tools to inform their “judgment of the likely or expected development” of syncope. However, the

literature is heavily dependent on both prospective and retrospective ED-based studies of variable quality and post-hoc registry studies. The extensive heterogeneity of studies cited in systematic reviews and meta-analyses further clouds the crystal ball of prognostication, with wide variation in study design, use of cohorts, definition of populations, and outcomes further hampering firm conclusions. Furthermore, in the context of high-quality studies, relatively little is known of prognosis in community dwelling patients who see only their primary care physician, and long-term prognosis has yet to be comprehensively assessed in a large-scale prospective study design in any setting. In addition, despite its absolute importance to patients, their care takers, employers, and teachers, recurrence has received much less attention than its terminally devastating counterpart mortality and needs much further work.

So, what is needed to convert the art of prognosis into something approaching a science? Is this indeed a possibility? While physician best judgement provides a better idea of prognosis than almost any of the available objective measures, currently it relies on a level of expertise and understanding that may not be part of the diagnostic lexicon of the majority of ED and primary care physicians seeing those with syncope, let alone others coming into contact with this patient group, from orthopaedic surgeons to immunologists. Nonetheless, given the mortality and recurrence rates above, it is critical that the syncope fraternity rises to the challenge of making prognostication as simple and accurate as possible, such that appropriate investigation, diagnosis, and management is launched regardless of the speciality the syncope sufferer presents to. However, the complex mosaic of underlying causative and contributory diseases, pathophysiologic and physiologic idiosyncrasies, pharmacologic contributors and predisposing circumstances does not make this an easy task.

3.9 What Makes Perfect Prognostication? Recommendations and Conclusions

The building blocks for better prognosis forecasting are rapidly falling into place. Risk factors for poor outcomes are much better understood than they were a decade ago, but are imperfectly applied in current tools, largely because of the heterogeneity of both patient characteristics and study design.

The initial task for researchers should therefore be definition. First, given the wide variation in causes (and hence outcomes) of syncope within them, patient groups need to be defined and studied rather than attempting a blanket view of syncope in toto. A good place to start is age, and the FAINT study has made a promising debut in this respect [24]. Second, outcomes need to reflect the totality of the syncope experience, incorporating not just serious medical outcomes like mortality, arrhythmias, major adverse clinical events (MACE), stroke and the like, but also the likelihood of recurrence. Third, more attention is needed for the vast number of syncopal episodes that present via non-ED services. Presentation to ED rather than

to a primary care physician (or no medical contact at all) frequently reflects patient, family, passersby, and even paramedic prejudices and individual beliefs and characteristics rather than the seriousness or otherwise of the cause of syncope. This much-neglected area needs significant focus. Fourth, outcomes in non-cardiac syncope are little studied. A recent systematic review and meta-analysis found only four studies with the methodological rigour to warrant inclusion, though this analysis was somewhat flawed in its use of a mixed view of non-cardiac and unexplained syncope [25]. The findings, that such syncope was associated with poor long-term outcomes (at 4.4 years) in those who were older or had diabetes or hypertension [25], need further exploration in prospective studies, particularly as current received wisdom is that (accidents notwithstanding) non-cardiac syncope carries a benign prognosis. Fifth, the dearth of information on long-term outcomes is of enormous concern. Cancer studies routinely discuss five-year survival, but there are no such data in syncope, despite the potential for a one in five chance of death at 4.2 years [22, 23]. Finally, while prognosis and hence risk stratification have been studied for more than a decade, there is no information on whether knowledge of prognosis influences outcomes. This seems intuitively obvious but has yet to be demonstrated systematically. When these factors are addressed and refined, we will be in a much better position to provide our patients and clinicians with an accurate prognosis that makes risk stratification and targeted investigation and management strategies based on it of benefit to them and the health care system as a whole.

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Chapter 4

The Economic Impact of Syncope: Direct and Indirect Costs



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4.1 Introduction

In the field of healthcare economics, cost-of-illness (COI) is a frequently employed concept that describes a range of outcomes in a population. This includes incidence or prevalence of a disease, its effect on morbidity and mortality, as well as direct and indirect economic costs. Direct costs include the costs of delivering clinical care, while indirect costs encompass the expenditures that result from premature death, disability or injury due to corresponding disease, and/or its comorbidities as well as the psychosocial impact and decrease in quality of life. Knowledge of COI for a given disease is critical for several reasons. It allows for rational formulation of public policy, helping to unveil cost inefficiencies and targets for improvement. In addition, COI is often leveraged to argue for increased resources being deployed to study or address a particular disease. Lastly, COI is important to define baseline cost and the impact certain interventions have [1].

The economic impact of syncope is substantial. In this chapter, the direct as well as indirect costs of syncope will be discussed. First we will review the epidemiology of syncope and how the incidence and prevalence are translated into various types of clinical encounters. We will then review direct estimates of costs associated with syncope, borne by healthcare payers. Much of this data will help us understand the types of clinical encounters and decisions that contribute to the cost. Next, our attention will turn to the less quantifiable but no less important indirect costs of syncope, both to the individual as well as society at large. Finally, this chapter will end with an overview of strategies to decrease both the direct and indirect costs of syncope.

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4.2 Syncope Burden

Syncope is common and generates a significant share of clinical encounters in the USA and Europe. An in-depth discussion of the epidemiology of syncope is beyond this chapter, however, prevalence has been reported to be 19–41% with a recurrence rate of 13.5% [2, 3], and an incidence rate of 0.80–0.93 per 1000 person-years [4].

Given the epidemiology, as well as the real and perceived danger of syncope and the spectrum of underlying pathology, it is not surprising that emergency visits for syncope are frequent. In the USA, syncope is estimated to account for 1–3% of all emergency department (ED) visits [5–7]. In a study that analyzed a sample of all US emergency departments, the admission rate was 32%; 10% in younger patients (age <40 years) and 60% in older patients (age >60 years) [5]. In a contemporary review [6], Sun et al. reported widely varying rates of admission between international regions and diverse cohorts in Australia, Canada, France, Italy, Japan, the United Kingdom, and the USA with a range of 12–83%. Overall, in the USA, syncope was estimated to account for 0.6–1.5% of all hospitalizations [4, 8]. In an analysis of the US Nationwide Inpatient Sample (NIS), from 2004 to 2013, Anand et al. found that the absolute number of hospitalizations for syncope in the USA actually has fallen in this time period by 42% from an estimate of 253,391 to 156,820 admissions. The mean length of stay also decreased from 2.88 to 2.54 days [7]. Updated data were accessed from the NIS and is shown in Fig. 4.1 These trends may reflect the increasing utilization of decision tools in the ED to avoid admissions as well as the increasing popularity of observation and/or syncope units. However, this decrease in hospitalizations has not correlated yet with a decrease in charges and costs (see below).

Further contributing to the number of acute encounters and hospitalizations for syncope is the substantial readmission rate. In a study analyzing the US National Readmissions Database from 2013 through 2014, the 30-day readmission rate for syncope was 9.3%. The most common cause for readmission was recurrent syncope (7.9%) [9]. In an analysis of the California Statewide Inpatient Database, 23% of all syncope admissions were for recurrent episodes [8].

4.3 Direct Economic Costs

The direct economic impact of syncope, like any other disease or syndrome, is difficult to estimate accurately. A variety of methods are employed, each with their benefits and drawbacks. In addition, a distinction must be drawn between charges and actual reimbursed costs. Syncope is a particular challenge because it is often conflated with other non-syncopal conditions that cause falls and injuries [10, 11]. Despite these caveats, a number of studies have sought to quantify the direct economic impact of syncope.

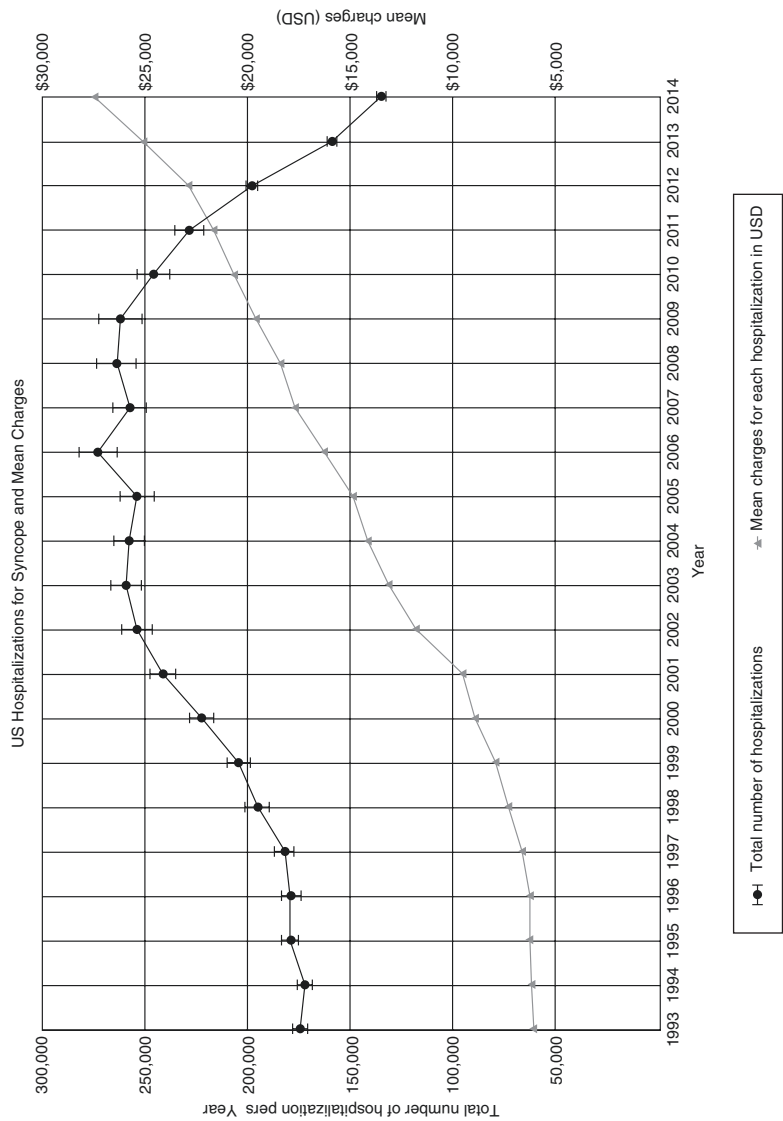


Fig. 4.1 US hospitalizations for syncope and mean charges. Total number of hospitalizations for syncope and mean charges in the USA over time. Recently, the number of inpatient hospitalizations has decreased while mean charges per hospitalization have continued to rise. Data were derived from the National Inpatient Sample from the Healthcare Cost and Utilization Project [13]

To facilitate comparisons between different regions and time periods, all costs cited in this chapter have been converted to 2019 United States Dollars (USD) and are included in parentheses after the unadjusted figure. Currencies were converted to USD based on the median exchange rates of a given study period. Dollar amounts from previous studies were corrected for inflation using the U.S. Consumer Price Index.

4.3.1 USA

In the USA, the NIS has been recently analyzed to estimate national hospitalization-related charges for syncope. From 2004 to 2013, despite a decrease in rate and duration of hospitalization for syncope, there has been a significant increase in cost as measured by hospital charges. Mean charges increased from \$17,514 to \$25,160 (\$19,257 to \$27,664, 2019) or by 43.6% [7]. Updated and expanded data from the NIS from 1993 to 2014 are shown in Fig. 4.1. This increase in cost per hospitalization may reflect increased utilization of diagnostic testing, macroeconomic trends in the cost of healthcare, increasing elderly patient population with significant cardiovascular comorbidities, and possibly a reduction in unnecessary admissions where the cost is low resulting in a shift in the mean due to the remaining admissions where the cost is high. When considering the number of hospitalizations over this time period, these numbers suggest a total national charge of \$4.4 billion in 2004 (\$4.8 billion, 2019), slightly decreasing to \$3.9 billion in 2013 (\$4.3 billion, 2019). Figure 4.2 portrays the change in total national charge estimate over a larger range of time with updated data from the NIS. In another recent study, Joy et al. analyzed the California Statewide Inpatient Database from 2005 to 2011. During this time period charges per syncope admission rose by a factor of 1.5. Likelihood of higher charges were associated with (in decreasing order) implantable defibrillator placement, pacemaker implantation, and cardiac catheterization among procedures and Holter monitoring, electroencephalogram, and echocardiogram among non-invasive testing [8]. In an earlier study, Sun et al. estimated the direct costs of syncope hospitalization by utilizing charge to cost ratios from the Medicare database and applying them to the NIS. They utilized data from the year 2000, and estimated a cost per syncope admission of \$5400 (\$8032, 2019) and total national cost of \$2.4 billion (\$3.6 billion, 2019) [12]. However, these numbers may also underestimate the total direct cost of syncope as they do not account for observation or syncope unit care and ambulatory encounters and testing. In addition, all studies utilizing the NIS do not account for professional fees.

There is a dearth of national studies that estimate the total cost of syncope across the spectrum of clinical care. However, in an earlier study, Malasana et al.¹⁴ estimated the actual payments that were made for chief complaints of faint and fall in the state of Utah. The average payment received for each patient evaluation was \$2517 (\$3005, 2019) for faint and \$3200 (\$3821, 2019) for fall, resulting in an estimated yearly cost equal to \$90,901,958 (\$108,530,930, 2019) and \$351,959,040

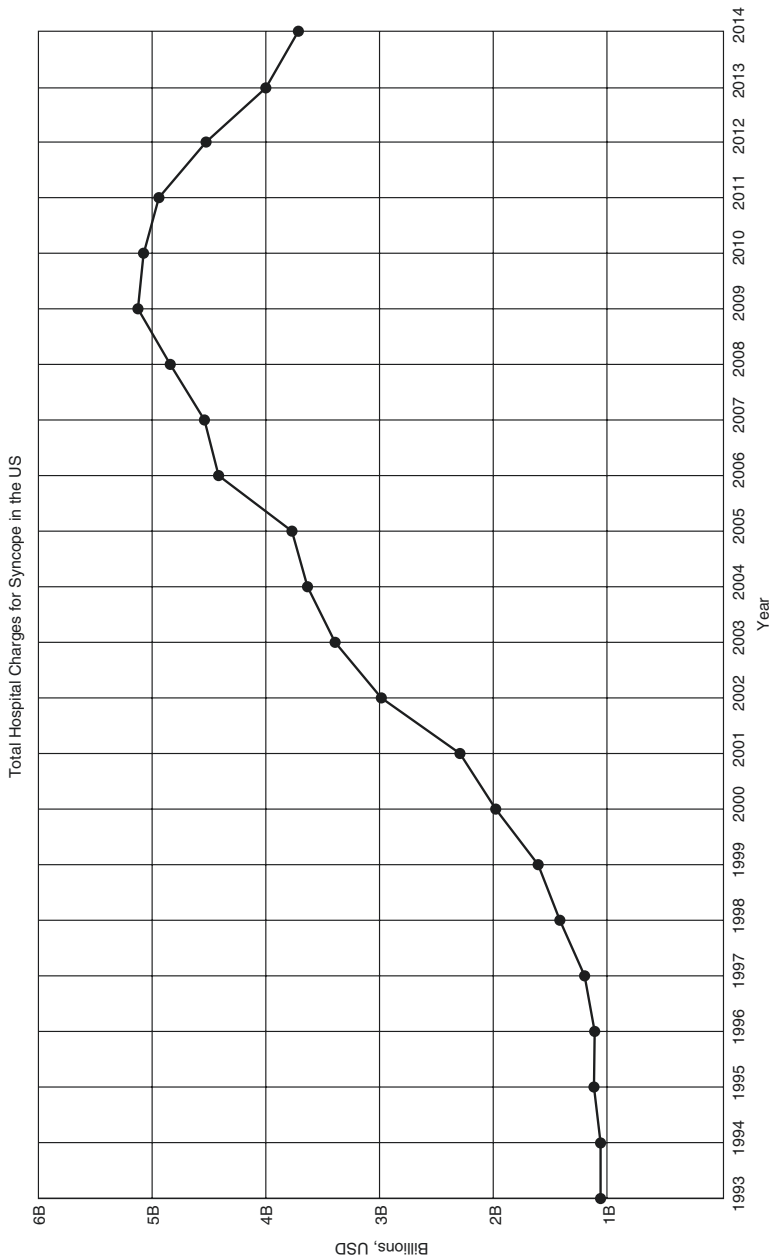


Fig. 4.2 Total hospital charges for syncope in the USA. Total charges for syncope hospitalizations in the USA over time. Total national charges had steadily rose until 2010, after which they have slowly decreased. Data are derived from the National Inpatient Sample from the Healthcare Cost and Utilization Project [13]

Table 4.1 Cost Analysis per Visit/Admission with Faint and Fall in the State of Utah

	Faint	Fall
Inpatient admission payment (\$)	12,640	19,194
Outpatient visit payment (\$)	499	366
Emergency department visit (\$)	1105	711
Mean payment (\$)	2517	3200
Payment per 1,000,000 inhabitants/year (\$)	33,224,400	128,640,000
Payment for the State of Utah per year (\$) (2,736,424 inhabitants)	90,901,958	351,959,040

Estimated payments made for faint and fall in the state of Utah in 2011 across the spectrum of clinical care, adapted from Malasan et al. [14]

(\$420,215,834, 2019), respectively. The results are depicted in Table 4.1, which demonstrate that hospitalization is an outsized contributor to cost. If these results are extrapolated to the US population (based on a population of 311 million inhabitants in 2011), then the estimated total national economic burden in direct costs would be greater than \$10 billion USD.

4.3.2 Europe

There have been several studies seeking to estimate the cost throughout Europe. In a small single-center study in Spain, the cost of admitting 203 patients to the cardiology unit for syncope was analyzed. The mean cost per patient was € 11,158 (17,531 USD, 2019) [15]. An estimate of the cost of syncope in Italy is derived from a study that compared a standardized pathway to a conventional pathway for syncope diagnosis. The overall cost per patient was € 1394 (\$1805, 2019) for usual care versus € 1127 (\$1454, 2019) for standardized care. Hospital costs accounted for 75% of the overall cost of care. If patients were diagnosed and discharged from the ED, the costs for usual and standardized care were only € 226 (\$292, 2019) versus € 198 (\$255, 2019), respectively [16].

4.3.3 Unexplained Syncope

Despite these considerable direct costs and economic resources that are dedicated to the clinical care of patients with syncope, the mechanism of syncope remains undefined in a substantial proportion of patients; uncertainty regarding mechanism asymmetrically contributes to cost, especially in conventionally managed patients. For example, in the California study by Joy et al. in 42.1% of patients admitted for syncope, the cause remained unknown upon discharge [8]. Even after outpatient testing and follow-up, the diagnostic yield generally remains low. In a study performed at the University of Utah, the rate of diagnosis of faint was 45% in a conventionally managed cohort after 45 days from the incident episode [17]. The PICTURE

study followed a prospective observational cohort of patients with unexplained syncope from 2006 to 2009 in 11 countries. Before the implantation of an implantable loop recorder, the median number of tests performed in this cohort was 13, with about half the patients receiving MRI/CT scans and 39% receiving EEG [18]. In a subsequent study, these data were integrated with per test cost estimates derived from a medical center in the UK. The calculated mean cost per testing in patients with unexplained syncope before implantation of an ILR was \$2563. A large amount of the cost was driven by repeat testing [19].

4.4 Indirect Economic Costs

The indirect economic costs can be conceptualized broadly and include the impact on both the patient and society. With regard to the patients, they may be subject to the loss of their personal productivity and earning potential due to unemployment, underemployment, or stigmatization. Patients may suffer from secondary injury and trauma, the costs of which are not captured by quantifying medical care directed towards syncope itself. Psychological illness and quality-of-life (QoL) impairment have both been correlated with syncope. Society at large must contend with the loss of productivity and the loss of a patient's contributions to society. In addition, depending on the characteristics of the regional healthcare system and the mix of payers, society often bears the economic costs in the form of taxation and/or higher health insurance premiums.

There are multiple studies that documented impairment across the domains of QoL. General tools to assess QoL such as the World Health Organization Brief Quality-of-Life Questionnaire as well as syncope-specific QoL assessments such as the Syncope Functional Status Questionnaire, among many others, have been found to consistently demonstrate that QoL is reduced in patients with syncope [6]. The degree of reduction in QoL has been compared to chronic conditions such as rheumatoid arthritis and chronic lower back pain. Female gender, higher level of comorbidity, presyncope, and recurrent syncope were associated with poorer QoL. Interestingly, in a recent analysis of patients enrolled in clinical trials for vasovagal syncope (VVS), QoL was observed to improve over time regardless of whether patients were in the treatment or placebo arms. This finding raises the question whether simply interacting with and being educated by specialists has an effect on QoL in patients with VVS [20].

Syncope has long been recognized to generally correlate with increased incidence of psychiatric illness. Patients with syncope have higher rates of anxiety, panic attacks, and depression. Those with affective disorders are more likely to experience recurrent syncope [21, 22]. VVS has been found to overlap with psychogenic pseudosyncope (PPS). In an analysis of records of patients referred to a syncope unit, 50% of patients with a final diagnosis of PPS had an initial diagnosis of VVS [23]. In another study, out of 23 patients diagnosed with mixed VVS/PPS, 83% of patients had an episode of PPS immediately following VVS induced by tilt

table testing. Both of these studies demonstrate that PPS and VVS can coexist and PPS may develop after an initial diagnosis of VVS.

Syncopal can affect a working patient's ability to remain employed and can cause workplace accidents and injury. First-time syncopal episodes occur frequently in adults of working age. In a recent Danish study using several nationwide population-based registries, the rate of workplace accidents associated with syncope as well the rate of termination of employment was analyzed. The 2-year risk of termination of employment was 31.3% in those who had a first-time syncopal event during employment, which was double the risk in the general population. Factors associated with termination in the syncope group were young age (<40 years), cardiovascular disease, depression, and a low educational level. In addition, patients with syncope were 1.4 times more likely to suffer workplace accidents. This risk increased an additional 1.4-fold in those with recurrent syncope [24].

Syncopal while driving has long been a concern in terms of safety for both the patient and other drivers. This topic is handled in more detail later in this volume. Understandably there is a societal interest to mitigate the potential harm from such episodes. Different governments and jurisdictions have varying laws and regulations in place to address the length of time a patient may not drive after a syncopal event. From a large case-control study of patients with syncope, 9.8% had an episode of syncope while driving. The elderly were more likely to have an episode. The most likely mechanism was reflex syncope [25].

In an analysis of Danish national registries, 4% of patients with a first-time syncopal diagnosis subsequently had a motor vehicle crash over a two-year period, double the rate of the general population. Separately, many patients with faint or fall secondary to syncope are misdiagnosed as having epilepsy or other neurological conditions [10]. They are thus subject to inappropriate treatment and medications such as anti-epileptic drugs with significant toxicities. They may be also subject to driving restrictions due to misdiagnosis. Similar restrictions are placed on patients with unexplained syncope since appropriate management and treatment have not yet been initiated.

4.5 Strategies to Reduce Cost

It has long been recognized that accurate and prompt diagnosis reduces costs, unnecessary testing, and mismanagement of syncope. As the guidelines discuss [10, 11], the first step is the exclusion of other causes of loss of consciousness. Once syncope is diagnosed, the mechanism should be sought in order to provide appropriate management. Initiation of mechanism-based therapy has tremendous impact on both direct and indirect cost [21]. Throughout the spectrum of clinical care of a syncope patient, unnecessary hospitalization and testing should be minimized (direct cost) while impairment of QoL should be recognized and mitigated (indirect cost). Several strategies have been studied and are reviewed below.

4.5.1 Emergency Department Risk Stratification

Often, the first healthcare encounter for syncope is in the emergency department (ED). In an effort to decrease the number of patients admitted to the hospital with syncope, decision algorithms have been investigated in order to risk stratify patients who may require admission and those who can be safely discharged. The San Francisco Syncope Rule (SFSR) [26], the Osservatorio Epidemiologico sulla Sincope del Lazio (OESIL) [27], and the Risk Stratification of Syncope in the Emergency Department (ROSE) rule [28] are three such examples. Although there is evidence that the adoption of these types of decision tools in the ED have decreased admissions to the hospital (as evidenced by our earlier discussion of trends in syncope hospitalizations and Fig. 4.1), they have had mixed performance in validation cohorts. Newer efforts are utilizing increased computational power and resource-intensive data techniques such as artificial neural networks to cost-effectively stratify patients with syncope [29].

4.5.2 Adherence to a Standardized Approach

Adherence to a standardized guideline-informed algorithm for the diagnosis and management of syncope has been shown to increase the rate of diagnosis, reduce hospitalizations, and unnecessary testing and cost. At the University of Utah, Sanders et al. [17] analyzed patients referred for faint to the institution's Faint and Fall Clinic (FFC) and compared them to patients with faint who had not been seen in the FFC. Patients seen in the FFC were managed according to a standardized algorithm that utilized point-of-care software to aid FFC providers in adhering to the algorithm. The standardized approach reflected the recommendations of the contemporaneous European and American guidelines on syncope [10, 11]. In the standardized group, only 4% of patients were admitted versus 20% in the conventional group. There was also a higher rate of diagnosis after 45 days and a lower number of tests and/or consultations in the standardized group (See Fig. 4.3).

4.5.3 The Syncope Unit

The syncope unit is a broad concept that encompasses a set of clinical resources dedicated to syncope that are applied in a standardized approach to the diagnosis and management of syncope and its mimics. The syncope unit has dedicated staff, infrastructure, and resources to deliver appropriate diagnostic testing and therapeutic intervention. In the SEEDS trial, intermediate risk patients were randomized to either evaluation in a syncope unit or standard care. The presumptive diagnostic

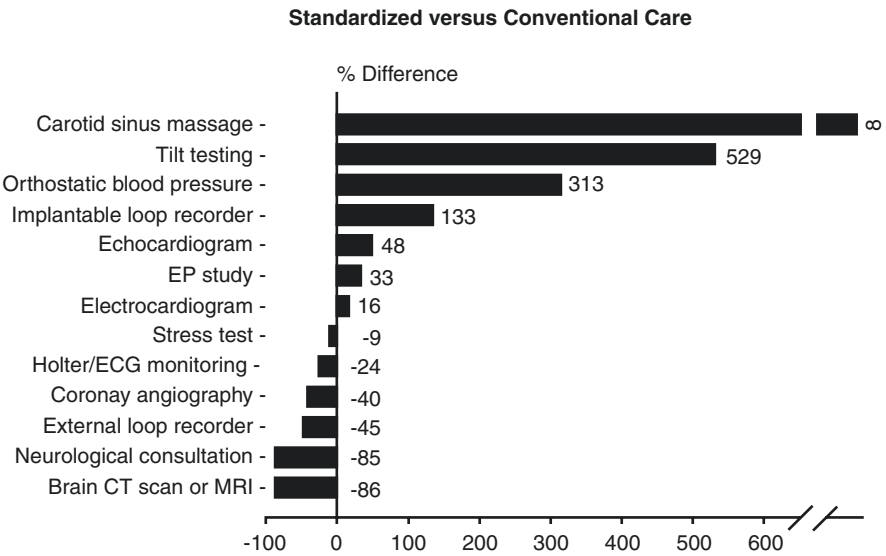


Fig. 4.3 Utilization of resources with standardized care [17]. Percent changes in test utilization in the standardized group versus the conventional group in patients with faint at the University of Utah

yield was significantly higher in the patients randomized to the syncope unit when compared to the control group (67% versus 10%). The hospital admission rate and total length of patient-hospital days were significantly lower in patients randomized to evaluation in the syncope unit. However, there was no difference in all-cause mortality or syncope recurrence rates over 2 years of follow-up [30]. In the 2018 ESC [11] guidelines for syncope, the European Heart Rhythm Association (EHRA) Task Force recommended the following targets in the evaluation of the effectiveness of a syncope unit: 20% reduction in undiagnosed syncope, 20% reduction in costs, less than 5% readmission rate, and less than 20% syncope recurrence within 1 year in patients who received a pacemaker for the treatment of syncope.

The syncope unit can have many forms from a consolidated physical structure to a decentralized “virtual” unit with a set of providers and resources dedicated to syncope but physically remote. Newer technology and the increasing utilization of advanced practice or non-physician providers have allowed for novel ways of conceptualizing the syncope unit or clinic. At the University of Wisconsin, a FFC was established at a geographically separate satellite medical campus, run solely by a nurse practitioner (NP). The NP was equipped with guideline-based software and teleconference access to a physician specialist at main campus. The NP risk stratifies patients, refers them for appropriate testing, interprets tilt table tests, and initiates appropriate therapy. In a recent study that compared the experience at the main campus with the NP-run clinic over a 6-month period, the diagnostic yield was the same at approximately 70%. In addition, the financial viability for the health system was analyzed. Total revenue exceeded expenses [31]. These findings may be

replicable on a larger scale, allowing for standardized guideline-based syncope care to be disseminated in a cost-effective way to areas where there is a dearth of specialists.

4.5.4 Implantable Loop Recorders (Insertable Cardiac Monitors)

The implantable loop recorder (ILR) also termed insertable cardiac monitor (ICM) has had a significant impact on the rate of diagnosis in patients with unexplained syncope and subsequently on the cost per diagnosis. In an earlier randomized control trial, patients with unexplained syncope were randomized to conventional testing with external monitor, tilt table testing, and EP study or to prolonged monitoring with an ILR over 1 year. Only 20% of conventional testing patients were diagnosed versus 47% in the ILR/ICM group. Cost per diagnosis was higher in the conventional group when compared with the ILR group (\$8414 vs \$5852) [32]. In the multisite European PICTURE study referred to earlier, after an observational cohort of patients with unexplained syncope received an ILR/ICM, a diagnosis was made in 78% of cases after 10 ± 6 months [18]. In a randomized trial from the UK including patients with recurrent syncope, the ILR/ICM cohort experienced improved QoL as measured by a visual analog scale for general well-being [33]. Studies have shown that ILRs are underutilized in the diagnostic workup for unexplained syncope and that the longer ILRs are kept in place, the higher the likelihood of a successful diagnosis and improvement in QoL, thus reduction in both direct and indirect costs, respectively.

4.5.5 Conclusion

The economic burden of syncope remains substantial. To better guide public policy, identify targets for intervention, as well as measure our progress in addressing cost, it is critical to continue to study the direct and indirect costs of syncope. More comprehensive estimates of cost across the spectrum of clinical care are needed. High indirect costs and impairment in QoL are common in patients with syncope and should be recognized by providers. Decreasing both direct (hospitalization cost and testing expenses) and indirect costs is contingent on obtaining an accurate diagnosis through a standardized approach informed by the guidelines. More advanced data methods such as machine learning, point-of-care software, telemedicine, and use of non-physician providers may also help further reduce cost, and expand cost-effective state-of-the-art syncope care in areas where it is much needed.

Conflict of Interest None.

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Part II

Basic Clinical Features

Chapter 5

Determining the Cause of TLOC/Collapse: The Initial Evaluation



Angel Moya and Patricia Fumero

5.1 Introduction

Syncope is defined, in both the recent ESC [1] and ACC/AHA/HRS [2] guidelines on syncope, as that form of transient loss of consciousness (TLOC) which is due to transient self-limited global cerebral hypoperfusion; TLOC may be initiated by many different causes. Therefore, if we want to make a correct diagnosis of syncope, it is essential not only to understand the concept and causes of TLOC but also how to perform the initial evaluation and differential diagnosis of the main clinical entities that can cause TLOC.

5.2 Definition and Classification of TLOC

Transient loss of consciousness is defined in both the ESC [1] and ACC/AHA/HRS [2] guidelines as a state characterized by self-limited loss of awareness and loss of responsiveness to stimuli (see also the Chap. 2 in this volume). In the ESC [1] guidelines there are some additional and complementary aspects such as short duration, abnormal motor control, and amnesia for the period of unconsciousness. In both documents the clinical definition of TLOC includes both real or apparent loss consciousness, because the initial clinical presentation may be similar in some cases in both conditions.

Each aspect of the definition is considered here:

- *Amnesia* implies that the patient is unable to remember anything that happens during the duration of loss of consciousness (LOC). Consequently, the only way to obtain information about the details of the episode is through eyewitnesses, if

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any were present. However, it must be considered that witnesses are not always able to provide reliable information about what has happened during the episode due to the fact that TLOC occurs unexpectedly and sometimes the witness is so startled as to not recall the event clearly.

- *Abnormal motor control* includes various situations, that sometimes may coexist:
 - *Fall*: When patients are not already in the supine position at the time of TLOC, they usually fall. Falls can be due to a loss of muscle tone or to muscular stiffness. Although the patient may not or cannot remember the fact of falling, he/she can usually recount being on the ground when regaining consciousness.
 - *Alterations in muscle tone* include both loss of muscle tone with flaccidity or an increase in muscle tone with stiffness. Some patients may present both alterations consecutively, usually first flaccidity followed by stiffness. This aspect usually cannot be explained by the patient and can only be described by a witness, despite the fact that it is not always easy to observe and describe.
 - *Movements* may or may not occur during episodes of TLOC. There may be absence of movements or the patient may have abnormal movements such as muscle jerks, seizures, head rotation, abnormally open or closed eyes. The presence of these abnormalities can only be obtained from eyewitness descriptions.
- *Self-limited* implies the concept of spontaneous recovery, without needing any medical intervention.
- *Short duration* has been arbitrarily established as 5 min representing the upper duration limit for true TLOC. An estimate of the duration of the episode cannot usually be obtained from the patient, but only from witnesses, and not infrequently the estimation of the duration is unreliable. Pseudo-syncope or pseudo-seizure events may last much longer than true syncope, but are technically not true TLOC (see the Chaps. 2 and 11 in this volume).
- *Loss of responsiveness* implies that the patient does not respond to verbal orders or tactile or painful stimuli. Obviously, absence of responsiveness can only be identified by a witness who has tried to interact with the patient during the period in which the victim has been presumed to be unconscious.
- *Real or apparent TLOC*. The inclusion of the term “apparent LOC” may seem to be contradictory. This concept is included in the definition because there are some clinical entities in which despite the absence of “real” LOC (e.g., pseudo-syncope), the clinical presentation may mimic true LOC, and the differential diagnosis with other causes of TLOC must be done at the initial evaluation.

5.3 Causes of TLOC

TLOC may be due to several different etiologies [3] (Fig. 5.1). The differences between them lie in the underlying pathophysiological mechanism (Table 5.1). The most frequent cause of TLOC is syncope [4, 5], followed by epileptic seizures [4] and psychogenic pseudo-syncope, the latter being in the category of “apparent LOC” [3].

Loss of consciousness due to head trauma, usually does not present problems of differential diagnosis, except in rare cases of patients who have presented an initial TLOC with secondary head trauma without witnesses; in those cases it may be difficult to determine if head trauma has been caused by LOC with collapse or if LOC is due to head trauma. In addition, there are other infrequent clinical entities, such as metabolic disorders, intoxications, or rare neurological conditions that can cause LOC (Table 5.2).

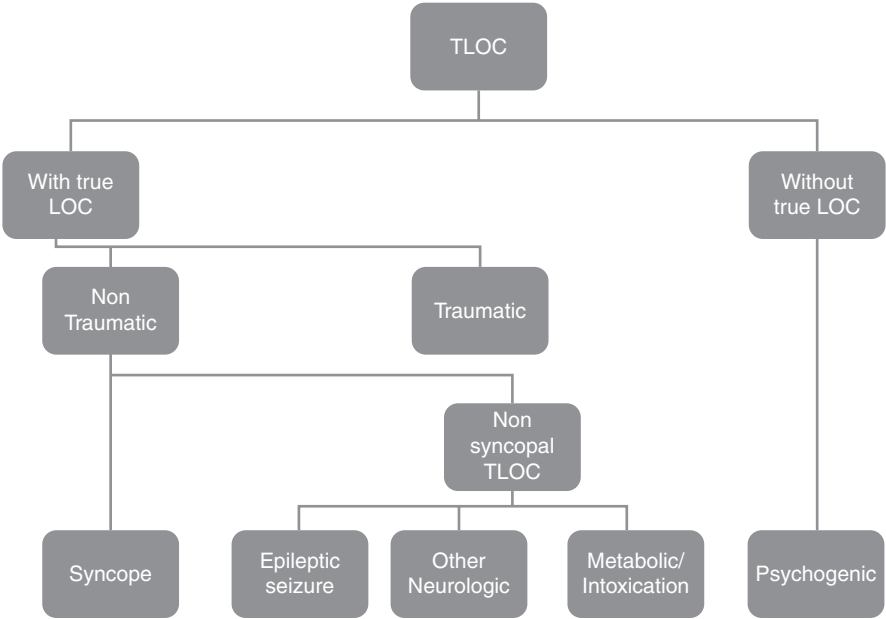


Fig. 5.1 Etiologies of TLOC. TLOC can be divided in true LOC or apparent LOC. Psychogenic TLOC, can manifest as psychogenic pseudo-syncope, when there are no movements or psychogenic non-epileptic seizures when apparent ‘seizure-like activity’ is reported to have occurred. True TLOC can be traumatic or non-traumatic. Of those non-traumatic, the most frequent is syncope, followed by epileptic seizures, and some less common rare neurologic or metabolic disorders. *TLOC* transient loss of consciousness, *LOC* loss of consciousness

Table 5.1 TLOC: Transient loss of consciousness

Clinical entity	Underlying mechanism
Syncope	Transient global cerebral hypoperfusion
Epileptic seizure	Excessive transient brain activity
Psychogenic TLOC	Process of conversion (so-called ‘conversion disorder’)

Table 5.2 TLOC: Transient loss of consciousness; TIA: transient ischemic attack; LOC Loss of consciousness

Clinical condition	Clinical characteristic of the episode
Generalized epileptic seizure [7]	TLOC lasting several minutes Generalized seizures from the beginning of the episode Memory deficit after the episode
Complex partial seizure	No fall (unless becomes generalized as described in Chap. 2) Unresponsiveness Later amnesia
Psychogenic pseudo-syncope	TLOC lasting several minutes High frequency of episodes, up to several times per week or day
Non-accidental fall	No real TLOC Responsiveness during the episode No amnesia during the episode
Cataplexy	Fall Flaccid paralysis Nonresponsiveness No amnesia
Intracerebral or subarachnoidal hemorrhage	Progressive loss of consciousness Other focal neurological signs or headache
Vertebrobasilar or carotid TIA	Focal neurological signs Usually without LOC (in cases with LOC, it is of long duration)
Subclavian steal syndrome	Focal neurological signs
Metabolic disorders (hyperglycemia, hypoxia, hyperventilation, hypocapnia)	Long duration Usually not LOC, but altered consciousness
Intoxication	Long duration usually necessitating medical intervention Usually not LOC, but altered consciousness
Cardiac arrest	Long duration of LOC No spontaneous recovery in most cases, need of resuscitation maneuvers for recovery
Coma	TLOC of long duration, usually needing treatment for recovery

5.4 Initial Evaluation of TLOC

The three main aims of the initial evaluation of patients who have presented with suspected TLOC are (Fig. 5.2):

1. Ascertain if the patient had true TLOC
2. If the episode is TLOC, diagnose the cause of TLOC
3. Perform a risk stratification

Herein we focus in points 1 and 2, as point 3 will be developed in other chapters.

Because TLOC is self-limited and short-lived, from which the patients recover completely, physical examination has virtually no role in determining the etiologic

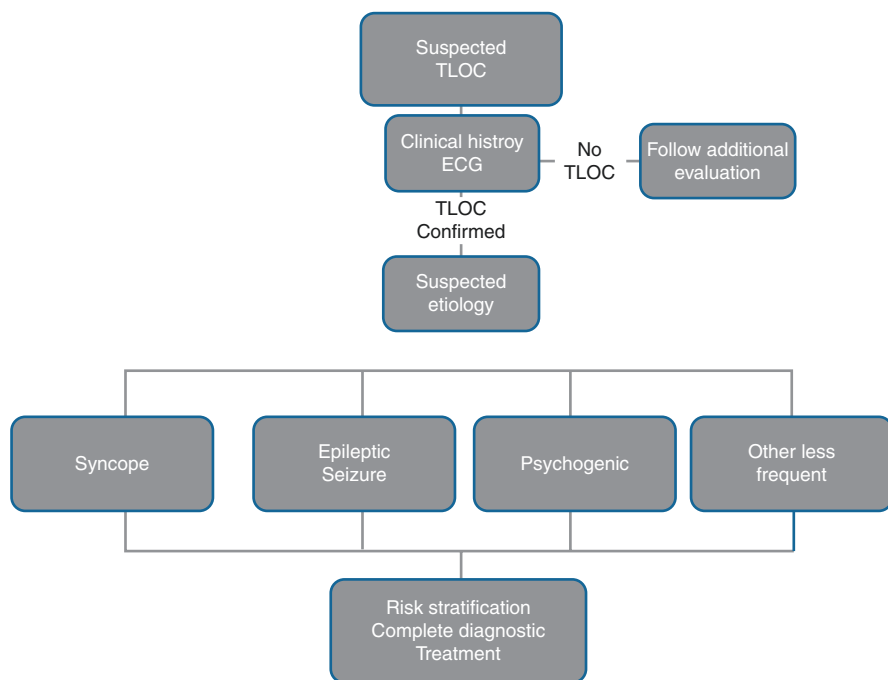


Fig. 5.2 Initial evaluation of patients with TLOC. In patients with TLOC, the initial evaluation should be done with the clinical history and the ECG. After this, in the vast majority of cases, it can be established whether it is TLOC or not, and if it is, to establish, with a high degree of suspicion, if it is syncope, epileptic seizure, psychogenic TLOC, or other less frequent clinical entity. Once the diagnosis of the cause of TLOC is established, risk stratification should be performed and diagnostic studies completed

diagnosis of the collapse, because in most cases when the patient is evaluated by a medical professional, the patient is fully recovered. For this reason, suspicion regarding the causal diagnosis can only be obtained by a careful clinical history either from the patient or from any reliable eyewitness, and on occasion with an ECG (e.g., acute myocardial infarction, suspected channelopathy, new complete heart block or long pauses). Physical findings such as heart murmurs, an irregular rhythm or vascular bruits can only be deemed to provide inferential information, not diagnostic. Several studies have shown that the clinical history is a useful tool in patients with suspected TLOC, and in the initial evaluation, the history and the ECG offer relatively high diagnostic accuracy [6–8].

A patient can be diagnosed with TLOC when all the clinical features that define TLOC, that is, short duration, self-limited, amnesia during the episode, abnormal motor control, and loss of responsiveness, are present. However, the presence of all these four aspects cannot always be confirmed. Only in those cases in which there is a witness during the episode and the witness is able to give details about the duration, the response to stimuli and motor control, can the diagnosis be confirmed. In absence of witnesses, the time duration and the responsiveness to stimuli usually cannot be assessed.

In the majority of cases, however, the diagnosis of TLOC is not difficult, because usually the patient indicates that he/she had experienced a fall, with a period of amnesia (i.e., they do not necessarily recall falling, but remember awakening on the ground). According to such a history, in absence of more detail from an eyewitness, TLOC can be considered likely when there is a clear gap in memory during which a fall occurred.

There are some situations in which it may be somewhat more difficult to ascertain whether there has been real LOC or not. It has been shown that a high proportion of elderly patients who have syncope, deny having lost consciousness; this makes the differential diagnosis between syncope and a non-accidental fall, which is a common situation in elderly population, difficult [9].

In those patients with suspected cardiovascular syncope, either due to the presence of an abnormal ECG, a history of previous structural heart disease, such as a previous myocardial infarction or a family history of sudden cardiac death, or in which other abnormalities are suspected such as pulmonary thromboembolism, the initial evaluation should include imaging tests such as an echocardiogram, a CT scan, or MRI [10].

In addition, in patients admitted to the emergency department with intermediate- or high-risk profile, ECG monitoring is recommended, for at least 12 h [11], and ambulatory ECG monitoring of high-risk patients up to 15 days should be considered [12]. The role of the most extended ECG monitoring in different clinical scenarios after the initial evaluation will be developed in another chapter (see Sutton and Benditt in this volume)

5.5 Recognizing the Cause of TLOC

Table 5.2 provides a detailed list of various clinical conditions that may be incorrectly diagnosed as syncope with some of the clinical characteristics of each of them. During the diagnostic evaluation of a patient with suspected TLOC, it is very important to keep in mind all these clinical conditions in order to accurately assess the differential diagnosis of syncope. Thus, the clinical history must include:

- Information about previous cardiac, neurologic, or psychiatric disease, as well as family history of sudden death.
- The absence or presence of triggers preceding the collapse and, if any, a description of their characteristics
- A detailed description of what happened during the episode: patients complexion color, absence or presence of movements, duration of the event, whether the eye lids were open or closed, if the tongue was bitten—which side or at the tip.
- Recovery status: was there a period of post-event fatigue or disorientation.

5.6 Risk Stratification

One of the most important aspects of the initial evaluation, especially in those patients without an etiologic diagnosis, is risk stratification. With the data obtained from the clinical history including not only the details of the syncopal episode but also from previous history, family history, ECG and physical examination, patients can be stratified as a low, intermediate, or high risk of having cardiovascular events or death at short or mid-term follow-up.

Low-risk patients can be discharged and referred to an outpatient syncope unit to complete the etiological diagnosis if deemed necessary, while intermediate- or high-risk patients are best admitted or evaluated in a specific observation unit. Patients evaluated in the emergency department should be referred to an outpatient syncope unit for follow-up.

5.7 Summary

This chapter has introduced the concept of TLOC and how it relates to syncope/collapse. The importance of clinical history findings that may be suggestive of the different etiologies of TLOC is emphasized; these same findings may prove crucial as well for risk stratification. Subsequent specific chapters as well as the Addenda of Practical Instructions of ESC guidelines [13] provide a detailed list of clinical aspects that should be addressed in each patient presenting with suspected TLOC.

Conflict of Interest No.

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Chapter 6

Seizures vs Syncope: Distinguishing Features for the Clinic



Robert S. Sheldon and Satish R. Raj

6.1 Introduction

Distinguishing between syncope and seizures in the cardiology or internal medicine clinic is a common problem that is highlighted in both of the recent ESC [1] and ACC/AHA/HRS guidelines [2]. The guidelines stress the importance of an accurate history, and recognizing the office time this might take we provide here a succinct and practical diagnostic and prognostic approach. Unfortunately, a medical history does not always successfully distinguish between epileptic seizures and convulsive syncope, and at times physicians revert to multiple diagnostic tests. The guidelines provide recommendations and we will review some of the evidence behind them. We will conclude with some practical tips on how to distinguish between convulsive syncope and epileptic seizures confidently in the office (Box 6.1).

6.2 Epileptic Seizures, Convulsive Syncope, and the Guidelines

Usually it is not difficult to distinguish syncope from epileptic convulsions. Syncope is a transient loss of consciousness due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery [1]. Most commonly there is little easily apparent muscle activity in syncope, whereas epileptic convulsions with collapse usually have tonic, clonic, or

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Box 6.1 Clinical Tips for Distinguishing Convulsive Syncope from Epilepsy

	Epilepsy	Convulsive syncope
Occurs supine	Common	Uncommon
Also has syncope and presyncope	Uncommon	Common
Typical prodrome: diaphoresis, presyncope, warmth	Uncommon	Common
Pallor	Uncommon	Common
Incontinence	Common	Uncommon
Muscle movement	Rhythmic, generalized	Pleiomorphic
Eye deviation	Lateral deviation	Fixed or upwards
Tongue biting	Common	Uncommon
Tongue bite location	Tongue side	Tongue tip
Prodromal cry	Common	Uncommon
Convulsion duration		Less than a minute
Post-ictal symptoms		Brief haziness, fatigue, diaphoresis, nausea

tonic-clonic muscle activity. Atonic epileptic seizures are uncommon and generally occur in the pediatric population. However, difficulties may arise, particularly in patients referred for specialized assessment. Convulsive activity is noted by casual bystanders in about 10% of faints, and careful videometric analyses of syncope induced in the laboratory [3] reported that up to 90% of faints are associated with some convulsive activity. This leads to initial referrals for assessment of epilepsy, and only later for help from cardiology clinics.

Generally the diagnosis of syncope or epileptic convulsions can be made with a careful history and physical examination. One ongoing significant problem is that despite a diagnosis of syncope, patients continue to be sent for investigations such as electroencephalography (EEG), computed tomography, magnetic resonance imaging, or carotid artery ultrasound [4]. The persistent use of such testing seems remarkable, given that syncope is due to transient global cerebral perfusion. The 2018 ESC guidelines [1] mention the overuse of these tests and narratively dissuade them, without a formal recommendation. In contrast the ACC/AHA/HRS guidelines [2] provide a firm Class III recommendation: do not perform these tests due to futility if the diagnosis of syncope is already made. There is clear evidence for the lack of usefulness [4].

Both the European [1] and North American guidelines [2] begin the diagnostic cascade with a patient having *apparent* transient loss of consciousness, which comprises syncope, epileptic convulsions, collapses generally due to psychological conversion syndromes, and uncommon causes such as cyanotic breath-holding in toddlers, cataplexy, falls without loss of consciousness, narcolepsy, cataplexy, and arrhythmias. The ACC/AHA/HRS guidelines [2] implicitly assume that a diagnosis of syncope has been made, while the ESC guidelines [1] provide a useful *aide memoire* in a table that lists conditions that may be incorrectly diagnosed as syncope.

Although these are all uncommon presentations, the table does provide a useful list of competing possibilities. Neither of the guidelines provide information at an early stage about sorting through the competing possibilities, although both variably return to some of the more important ones later in the documents. The first etiologies to be considered are syncope and epileptic seizures.

Both guidelines provide clinical definitions of syncope. The ESC [1] defined syncope as TLOC due to cerebral hypoperfusion, characterized by a rapid onset, short duration, and spontaneous complete recovery. Cerebral hypoperfusion is, however, a mechanistic insight and not a clinically useful criterion. In contrast, the ACC guidelines [2] define syncope as “a symptom that presents with an abrupt, transient, complete loss of consciousness, associated with inability to maintain postural tone, with rapid and spontaneous recovery. There should not be clinical features of other non-syncope causes of loss of consciousness, such as seizure, antecedent head trauma, or apparent loss of consciousness (i.e., pseudosyncope).” In keeping with the practice of most physicians, it defines syncope not just by what it is at the bedside and the clinical evidence in its favor, but also the evidence against it.

However, things are not always as simple as they seem, because convulsive syncope is quite common. Casual bystanders report seizure activity in 10% of faints, and careful videometric analysis of syncope induced by tilt table testing has reported transient seizure-like activity in up to 90% of faints (Tables 6.1, 6.2, and 6.3). This and the unwitnessed nature of many transient losses of consciousness trigger neurologic investigation in many patients. The ACC guidelines state that interictal electroencephalography, carotid artery ultrasound, brain MRI, and brain CT should not be performed in patients with syncope with unequivocal Class III recommendations on the basis of diagnostic futility. This was informed by a recent meta-analysis [4] that found only 2/6234 of these tests in patients with syncope provided a new, important, and unanticipated finding. Interestingly one or more of the tests were performed in 11–58% of syncope patients.

Table 6.1 Estimated prevalence of convulsions during syncope

Clinical scenario	Observation type	Seizure-like estimate (%)
Healthy subjects		
Blood donor clinic [5]	Chart review	12
Blood donor clinic [5]	Prospective observation	42
Physiology study [3]	Induction of syncope induction	90
Syncope patients		
Tilt table test [6]	Physiology study	4.4
Tilt table test [7]	Induction of syncope	8
Physiology study [3]	Induction syncope induction and observation	90
Tilt test [8]	Syncope induction and observation	90
Convulsive patients		
Tilt test [9]	Seizures with induced syncope (LAR)	53
Tilt test [10]	Seizures with induced syncope	40

Chart reviews of reported convulsive activity, and tilt test serendipitous observations, are probably more relevant to clinical experience

Table 6.2 Clinical observations during convulsive syncope [3, 5–7]

Clinical sign cluster	Observation
Skin	Diaphoresis
	Post event fatigue
	Pallor
Head and neck	Nuchal rigidity
	Fixed gaze
	Upwards eye deviation
Convulsive activity	Tonic spasms
	Brief clonic convulsions
	Generalized convulsions
	Focal seizures or deficits
	Tonic-clonic convulsions
	Myoclonic jerks, focal or multifocal

Table 6.3 Misdiagnosis rates in epilepsy due to syncope

Clinical setting	Misdiagnosis rate due to syncope
Treatment-refractory epilepsy [11]	6% on case review
Family practice and epilepsy clinics [12]	7% on case review
Epilepsy clinic [13]	13% on case review
Questionable or refractory epilepsy [14]	21% asystolic or bradycardic on ILR during seizure
Questionable or refractory epilepsy [15]	42% cardiovascular, of whom 27% vasovagal syncope on tilt tests
Questionable or refractory epilepsy [10]	40% positive tilt tests
Questionable or refractory epilepsy [9]	65% positive tilt tests
Questionable epilepsy [16]	65% positive tilt tests
Questionable epilepsy [17]	67% positive tilt tests

6.3 Epidemiology

Epilepsy The prevalence and incidence of syncope and epilepsy drive the difficulties that clinicians face in distinguishing syncope from seizures. A narrative review [18] reported that although estimates vary considerably depending on definitions, locale, detection, and diagnostic methods, the age-adjusted prevalence of epilepsy is 2–20 per 1000 people, and the age-adjusted incidence of epilepsy is 0.15–0.5 per 1000. Epilepsy is therefore relatively uncommon, occurring in no more than 1% of people and presenting in fewer than 0.1% of people per year.

Syncope In contrast to epilepsy, syncope is common, having a lifetime cumulative incidence over 50%. The likelihood of syncope by age 60 years is about 37% [19, 20], and many more faint for the first time as they age. In Malaysia [21] the cumulative incidence in the Malay, Chinese, and Indian populations aged about 65 years is 25–35%. Data specifically for older Malaysian populations are not available yet.

The yearly incidence of syncope is in the range of 1–6%. Taken together, syncope probably has a lifetime prevalence and yearly incidence that are roughly 10 to 50-fold those of epilepsy. Given the Bayesian nature of diagnosis, misclassifications are certain to happen, particularly in clinical settings that may suggest both syncope and epilepsy. Studies from Canada [13] and the UK [10] confirm this. An All-Party United Kingdom Parliamentary Group on Epilepsy reported in 2007 that 74,000 UK patients were being treated for epilepsy that they did not have. In Nova Scotia 13–25% of patients with an apparent diagnosis of epilepsy in truth had a diagnosis of syncope [13]. Zaidi et al similarly reported that 40% of epilepsy patients fainted on tilt tests designed to provoke syncope [15]. One of the challenges is the frequent association of convulsive activity with syncope [22]

Convulsive Syncope Convulsive syncope is more common than generally understood, leads to referral for epilepsy assessment, and is frequently misdiagnosed (Table 6.1). It has been studied clinically [5], induced by tilt table testing [6, 7], and recorded from implantable cardiac monitors (ICMs) [14, 15, 23]. Myoclonus is the most common kind of convulsive syncope, usually occurring near the onset of syncope and lasting seconds. It is often preceded by presyncope and its associated symptoms such as warmth and sweating. Prolonged convulsions and post-ictal confusion are uncommon.

Lin et al. [13] reported the type of convulsions and hemodynamics during vasovagal syncope induced by blood donations. Convulsions occurred in 12% of syncopal spells if studied retrospective and 42% in a prospective study. Tonic spasms with usually flexed elbows occurred in 66% of convulsive syncopal spells, accompanied by diaphoresis, pallor, upwards eye deviation, fixed gaze, and brief nuchal rigidity (Table 6.2). Recovery was rapid, occurring in less than 30 s, and mild confusion occurred in recovery. A few patients had brief clonic convulsions, violent myoclonic jerks, and rarely severe convulsive activity causing injury and requiring restraint. Hypotension and bradycardia were similar in convulsive and non-convulsive syncope.

Lempert et al. [3] deliberately induced transient cerebral hypoxemia and syncope in 42 healthy subjects subjected to a “fainting lark” maneuver. This maneuver is a combination of hyperventilation in a squatted position, rapidly standing up, and performing a Valsalva maneuver. Myoclonus occurred in up to 90%, with multifocal arrhythmic jerks in proximal and distal muscles (Tables 6.1 and 6.3). Generalized myoclonic movements included head posturing, oral automatisms, and righting movements. The eyes often remained open and initially were deviated upwards. Although these were unusual physiologic circumstances the sequence of events resembles that seen in convulsive syncope induced by blood donation.

Song et al. [14] studied myoclonus that accompanied vasovagal syncope induced by tilt testing. Only 10/226 (4.4%) patients who fainted had seizure-like activity (Table 6.2), but there was a range of presentations. Five had multifocal myoclonic jerking, and five had unifocal myoclonic jerky movements. Similarly Passman et al. [15] reported 18/222 (8%) positive tilt tests with convulsive activity. Eleven patients (5%) had tonic-clonic activity, three had focal seizures, and one each had dysarthria, aphasia, unilateral extremity dysesthesia, and temporal lobe epilepsy symptoms (Table 6.1).

The prevalence varies depending on the situation. About 6% of syncope induced by tilt testing is associated with convulsions [6, 7], and 12–42% of blood donor patients have convulsive syncope [5]. The higher prevalence during the fainting lark maneuvers and the prospective studies may be due to increased observer attention to clinically irrelevant movements. The pleiomorphic types of convulsions associated with syncope might be a challenge to accurate diagnosis.

Convulsive Syncope Misdiagnosis Several groups have examined the misdiagnosis rate in populations of patients thought to be epileptics (Table 6.1). Josephson et al. [9] reviewed 1506 consecutive out-patient epilepsy referrals and found that 13% in truth had vasovagal syncope. Smith et al reported [12] a misdiagnosis rate of 26% in 184 patients referred for management of treatment-refractory epilepsy. Of the 184 patients 7% in fact had syncope. Finally, Chowdhury et al. [18] reported a narrative review of six publications that reported epilepsy misdiagnosis rates from 1998 to 2007. The studies included both family practices and epilepsy clinics. The overall misdiagnosis rate was 20%, with patients diagnosed by neurologists having the lowest reclassification rate. The causes of misclassification varied widely, and syncope accounted for 25–35% of the true diagnoses.

6.4 Useful Features in the History

General Comments The medical history is the foundation of an accurate diagnosis. However, given the important role of pattern recognition in establishing a diagnosis, physicians frequently disagree. Each patient presents with an idiosyncratic collection of symptoms, described with an idiosyncratic weighting and description. Some diagnostic factors are more common than others. Establishing an etiologic diagnosis for syndromes of loss of consciousness can be particularly difficult because the principal symptom is unconsciousness (making getting a history of the spell from the patient problematic), and bystander histories may not be available or precise. The Fainting Assessment Study investigators, who had deep physiologic and diagnostic experience with syncope, reported that only 24% of patients had a definite diagnosis after the initial encounter [24].

Syncope Syncope has numerous potential causes and classifications (Box 6.1). A particularly useful classification appears in the European Society Guidelines [1] 2018, whose highest level classification includes reflex syncope, syncope due to orthostatic hypotension, and cardiac syncope, almost always due to abrupt bradycardia or abrupt tachycardia. In the community, vasovagal syncope is the most common, and quite benign, diagnosis. Conversely, syncope due to cardiac tachyarrhythmias, heart block, or valvular disease might be prevented with appropriate detection and treatment [1].

Distinguishing between syncope and epilepsy depends to some extent on the cause of syncope, because these are often easily recognizable. For example, initial

orthostatic hypotension often presents with syncope within 15–20 s of standing up and walking a few feet to a nearby destination such as the kitchen or bathroom. Similarly, vasovagal syncope due to exposure to needles, blood, carnage, and so on—the so-called blood/injury fear syndrome—is easily recognized. The third very common pattern is vasovagal syncope that occurs with quiet sitting, standing, or walking for at least 1–2 min. Common presentations include patients who faint in church, while standing at attention, or in hot environments such as showers. Syncope associated with classic orthostatic hypotension usually includes a history of frequent presyncope that is worsened by longer periods of upright posture, and syncope itself is much less common than presyncope. Often there are other classic symptoms of autonomic failure such as dry mouth, heat intolerance, lack of pilo-erection, bladder and bowel dysmotility, and other manifestations of synucleinopathies. Patients with cardiac syncope usually lack a prodrome other than brief palpitations, and usually have a history of some form of electrical or structural heart disease and ECG abnormalities.

The most important feature that distinguishes syncope from seizures is that syncope patients are usually limp, while patients who seize have convulsive activity with characteristic presentations, other than in rare childhood cases. Depending on the cause of syncope there may be a prodrome consisting of progressive presyncope, visual blurring, a vague sense of malaise, diaphoresis, and a terminal flushing warmth [25]. Syncope itself usually lasts less than a minute, although some patients may take several minutes to fully regain consciousness. After regaining consciousness vasovagal syncope patients may be quite tired for minutes to days.

Epilepsy Generalized tonic-clonic convulsions are the most commonly recognized seizures causing loss of consciousness (Box 6.1). The diagnostic features of epilepsy depend on the type of epilepsy, but when considering a diagnosis of syncope versus epileptic seizures the patient while fainting is usually limp, while the patient with epilepsy usually convulses. Atonic epileptic seizures are quite uncommon and occur only in children [26]. Specific triggers are less common in epilepsy than in syncope. Similarly specific auras are less common than might be thought. Convulsions tend to be rhythmic, severe, and bilateral. Useful diagnostic clues include a history of lateral tongue biting and bedwetting [27]. This diagnostic point requires careful questioning, because many syncope patients also report post-spell confusion. Complex partial seizures, or temporal lobe epilepsy, may not be associated with generalized convulsions. Petit mal or absence attacks in the young usually do not result in collapse. Epileptic convulsions last longer than faints, and are often followed by significant and prolonged post-ictal disorientation and confusion. The latter is minor and brief after faints.

Structured History Agreement among three neurologists about seizure diagnosis was improved by structured diagnostic criteria [28], implying that unstructured criteria lead to diagnostic confusion. The importance of historical features in distinguishing among causes of syncope was confirmed later [29, 30]. Accordingly, diagnostic point scores were developed to address these questions.

A point score was developed by three academic centers in Canada and Wales [27]. The causes of loss of consciousness included various types of epilepsy, vasovagal syncope, and cardiac arrhythmias. The point score distinguished between syncope and seizures [27] with a sensitivity of 94% and a specificity of 94%. Significant historical aspects suggestive of seizure activity included preceding emotional stress, déjà vu or jamais vu, head turning or unusual posturing or motor activity during an event, confusion upon awakening, or tongue laceration. Syncope was favored by separate episodes of presyncope, preceding diaphoresis, or events precipitated by prolonged standing or sitting or exposure to medical settings. The point score was independent of the number of losses of consciousness and length of history, suggesting that it could be used quite early in the patient's clinical course. The point score functioned in the same fashion as a skilled clinician, weighing the evidence both for and against competing diagnostic possibilities.

There were three significant limitations. First, older patients lose many of the autonomic symptoms associated with vasovagal syncope, which numerically dominates the syncope population. Second, the study only included seizure patients with diagnostic EEGs and either generalized convulsions or complex seizure. Third, and critically, the study did not include patients with convulsive syncope, and this is the group that poses the biggest challenges. However, the syncope versus seizure score has proven useful in complex cases where the diagnosis of convulsive syncope versus epileptic convulsions has been difficult. Some simple clinical observations that can distinguish between convulsive syncope and epileptic convulsions are presented in Box 6.1.

Convulsive Syncope Vasovagal syncope is commonly associated with brief seizure activity. Generally myoclonic convulsions occur in the first 10–15 s of syncope and spontaneously resolve. Although on tilt tests the most common seizure activity is fixed staring, extensor rigidity, and tremors the range of documented movements is wide. Usually the diagnosis can be made by asking whether the patient convulses at other times, whether the convulsions are preceded by a prodrome similar to that preceding syncope, whether the convulsions culminate in syncope, and whether they are followed by the same constellation of symptoms that follow syncope. A bystander history can be very helpful. In short, take a scrupulously careful and iteratively inquisitive history.

6.5 Tilt Tests for Questionable Epilepsy

Tilt table testing has been shown to be of value in this clinical setting when a detailed history cannot clearly determine whether the convulsive movements were secondary to syncope, given the need for objective evidence to help distinguish this entity from true epileptic seizures. The ACC guidelines [2], although generally conservative in recommending the use of tilt tests, provide a Class IIA recommendation for the use of tilt tests in suspected cases of convulsive syncope. Several studies reported

the utility of tilt tests in providing diagnostic clarity in patients with a history of epileptic seizures, but with spells of uncertain etiology, according to the consistent findings of five studies (Table 6.3). Sabri et al [16] analyzed the results of 40 young patients (under 21 years) who had an initial diagnosis of epilepsy, mostly complex partial seizures, but whose diagnosis was challenged following case review by neurologists. Tilt testing was positive in 65% of patients. Interestingly, almost all the study patients had clinical factors that were consistent with either vasovagal syncope or initial orthostatic hypotension. Grubb et al. [27] subjected 15 patients with recurrent unexplained seizure-like episodes that were unresponsive to antiepileptic medication to tilt testing. Over 67% had syncope and tonic-clonic seizure activity induced by tilt testing, and associated with hypotension and bradycardia. The EEGs showed diffuse brain wave slowing consistent with brain hypoxia in five patients during the convulsive episode. Diffuse brain wave slowing is a typical finding during syncope induced by tilt testing [31]. Zaidi et al. [11] subjected 74 adult patients with apparently epilepsy who were either refractory to antiepileptic drug treatment, or whose diagnosis was subsequently challenged on clinical grounds. A cardiovascular diagnosis was established in 42% of patients, including vasovagal syncope in 27%. Taken together these studies indicate that 50% of patients with questionable or drug-refractory epilepsy have vasovagal syncope rather than epilepsy. Given the incomplete sensitivity of tilt testing, it may be that most patients with questionable or drug-refractory epilepsy actually have syncope as their true diagnosis.

6.6 Neurologic Investigations

Imaging of the brain and its vasculature is performed surprisingly commonly in the assessment of syncope, especially in light of the fact that syncope is due to global cerebral hypoperfusion. A recent meta-analysis [4] reported that magnetic resonance imaging, EEGs, carotid artery ultrasound, computed tomography, and were performed in 11%, 17%, 18%, and 57% of cases, respectively. Taken together, they provided new and informative results in only 2/6334 tests. The ACC provided Class III recommendations on the basis of futility.

6.7 Video Recordings

Direct video recordings of transient losses of consciousness offers considerable promise. It has proven quite accurate in diagnosing epilepsy and pseudoseizures. Might video recordings during tilt testing offer similar hope? Several case series reported the use of video recordings, to establish the diagnosis of syncope with a combination of EEG recordings and tilt test results [32]. The ESC 2018 guidelines provide a Class IIa recommendation for home video recordings of syncope, and a Class IIb recommendation for video recording of tilt testing. There is limited

evidence behind these recommendations. LaRoche et al [9] reported that 11/17 patients with refractory suspected epilepsy had positive tilt tests with EEG and videometric recordings, but the contribution of the video recording was not specified. Similarly Ninni et al [10] reported that 59/101 patients with possible convulsive syncope or epilepsy had positive tilt tests with EEG and videometric recordings, but the contribution of the video recording was not specified.

6.8 Implantable Cardiac Monitors for Questionable Epilepsy

Implantable loop recorders (ICMs) also known as insertable loop recorders (ILRs) document the ECG findings of events that occur sporadically and infrequently, such as syncope. Other technologies such as ambulatory electrocardiography and external event recorders have a low rate of diagnosis due to the infrequent nature of events such syncope. The European Heart Rhythm Association issued guidelines for the indications for ICMs in the assessment of syncope [33]. The guidelines, recognizing the paucity of evidence of the ability of ICMs/ILRs to distinguish syncope from epileptic seizures, recommended their use here as Class IIB, Level C.

Given that much of vasovagal syncope is associated with sinus rhythm or sinus bradycardia, and epilepsy associated with sinus rhythm, using an ICM/ILR might not seem a promising approach. The largest study to date was REVISE [14]—Reveal in the Investigation of Syncope and Epilepsy—which reported the results of ICM/ILR assessment of 103 adult patients with definite or probable epilepsy. The patients were included if they were drug-refractory or if clinical reassessment cast doubt on their diagnoses. Fully 65% had a transient loss of consciousness that was associated with ECG documentation, and 22 patients (21%) had asystole or profound bradycardia. Given that at least half of syncopal spells documented by ICM/ILR in syncope patients are associated with normal sinus rhythm the total misdiagnosis rate in the REVISE study might be as high as 60–70%. Therefore the accumulated ILR data indicate that at least 20% of patients with a questionable diagnosis of epileptic seizures may actually have convulsive syncope due to bradycardias, and the true prevalence of convulsive syncope in this population might be much higher.

6.9 Conclusions: A Practical and Efficient Approach

It is not usually difficult to distinguish syncope from an epileptic convulsion (Box 6.1). Patients who faint usually have a characteristic prodrome if they are middle aged or younger, are motionless much of the time while unconscious, and are pale, damp, or nauseated afterwards. Patients with epileptic convulsions often have tonic-clonic convulsions, or a Jacksonian progression, or have a recognizable prodrome of posturing or a sense of déjà vu. There are many other signs and symptoms that can help distinguish between syncope and epileptic convulsions.

The biggest difficulty is in determining whether patients have convulsive syncope or an epileptic convulsion. Here, the main tool is a fastidious history. A careful, perceptive, evidence-based history is essential, and bystander observations are important. The main points in favor of convulsive syncope include fainting at other times, the ability to match the prodromal symptoms between the two, and only brief convulsions lasting a few seconds at the beginning of the transient loss of consciousness. Often convulsive syncope is followed by signs and symptoms that follow syncope. Most commonly convulsive syncope comprises brief extensor rigidity and tremors, but not infrequently there are seemingly unlikely motor movements that can resemble brief choreoathetosis. Tilt tests despite their limitations appear to be quite useful in many patients. Finally, excellent communication between neurologists and internists or cardiologists probably offers the best chance for accurate diagnoses.

Epilepsy in comparison is often more prolonged, has its own characteristic set of signs, and usually has a chronic presentation. Both guidelines recommend tilt table testing, if possible with EEG and videometric recordings, to distinguish between the two in the uncommon case where a good history does not suffice. Given the much higher incidence of syncope, and the complications associated with antiepileptic drug therapy, caution should be used in empirically treating undiagnosed transient losses of consciousness as epileptic convulsions.

Conflict of Interest The authors have no conflict of interest to declare.

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Chapter 7

Reflex Syncope: The Common and Less Common Variants



Ritsuko Kohno and Haruhiko Abe

7.1 Introduction

This chapter describes the nature and management of the various forms of reflex syncope based on the 2017 American College of Cardiology, American Heart Association Task Force on Clinical Practice guidelines, and the Heart Rhythm Society (ACC/AHA/HRS) guidelines for the evaluation and management of patients with syncope [1] and the 2018 European Society of Cardiology (ESC) guidelines for the diagnosis and management of syncope [2].

The reflex syncopes include vasovagal syncope (by far the most common), carotid sinus syncope, and various so-called situational syncope syndromes. Table 7.1 provides a more detailed classification of the members of the reflex syncope category.

Reflex syncope comprises a transient loss of consciousness caused by neural reflex bradycardia and/or vasodilation [3]. As currently understood, regardless of the specific trigger, certain basic central nervous system elements are common to all forms of reflex syncope: specifically, the nucleus of the solitary tract in the brainstem is activated indirectly or directly, leading to increased activity of the parasympathetic nervous system and decreased activity of the sympathetic nervous system. The outcome may be any of several hemodynamic responses (Fig. 7.1); these are classified as follows: (1) cardioinhibitory: which leads to syncope due to bradycardia but without excessive vasodepression; (2) vasodepressor: which leads to syncope due to transient vascular dilation leading to hypotension without bradycardia; and (3) mixed: which involves to varying degrees both bradycardia and vasodepression. The ‘mixed’ form is the most commonly encountered. However, from episode to episode, patients may not always show the same hemodynamic pattern.

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Table 7.1 Classification of reflex syncope

Reflex syncope
• Vasovagal syncope
• Carotid sinus syndrome
• Situational syncope
– Micturition
– Defecation
– Swallow/deglutition
– Cough
– Laughter/gelastic
– Others
Syncope after exercise
Syncope after sneezing
Syncope after playing a brass instrument
Syncope after weightlifting
Post-prandial syncope

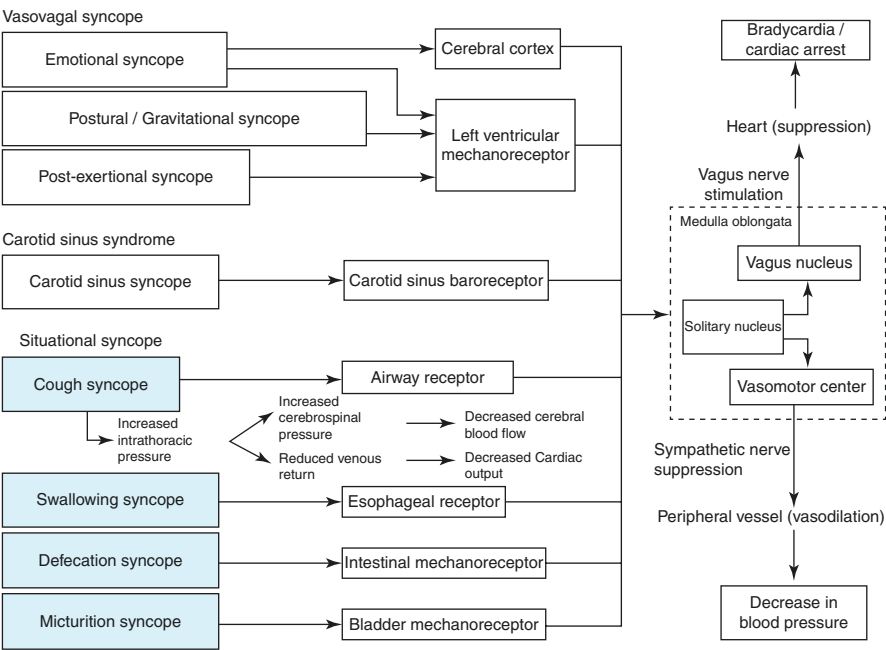


Fig. 7.1 Schematic illustration of the neural reflex pathway in reflex syncope. Reproduced from the Guidelines for Diagnosis and Management of Syncope (The Japanese Circulation Society) [4, 5]

Syncope usually occurs when the affected individual is sitting or standing, and in the case of reflex faints, it may be accompanied by a prodrome such as feeling hot or cold or nauseated, or visual disturbances (e.g., flashing lights, curtain falling). Treatment of reflex syncope includes the avoidance of triggers and if that fails, the assumption of physical postures for prevention of hypotension and restoration of

cerebral blood flow when the initial symptoms occur (e.g., lying down, squatting). In any case, loss of consciousness alone usually does not cause permanent damage to health, but physical injury due to a collapse may be serious.

7.2 Types of Reflex Syncope

7.2.1 *Vasovagal Syncope (VVS)*

7.2.1.1 Clinical Features

Vasovagal syncope (VVS) may be triggered by prolonged standing or sitting, painful stimulation, insomnia, fatigue, mental stress (e.g., fear), physical stress, or environmental conditions, such as dehydration or being in a crowd or enclosed space. Often there is no identified trigger. Many patients experience headache, double vision or visual grey-out, nausea, vomiting, abdominal pain, a “blackout,” or other symptoms immediately before VVS [6–8].

Vasovagal syncope rarely occurs when patients are moving; instead, it mostly occurs when they maintain the same posture (e.g., standing or sitting) or have just stopped vigorous exertion. VVS occurs most often in the morning when body hydration may be at its nadir for having not consumed fluids during the sleeping hours. The duration of unconsciousness is relatively short (less than 1 min), with no sequelae other than potential trauma that can occur when patients fall. The prognosis of VVS is good from a mortality perspective [9].

7.2.1.2 Pathophysiology

The pathophysiology of VVS remains unclear and a comprehensive discussion lies outside the scope of this chapter. However, it is generally believed that prolonged standing and sitting causes congestion in the peripheral and splanchnic veins, reduces venous return to the heart, and decreases cardiac output, leading to lower arterial pressure and activation of baroreceptor reflexes in the carotid sinus and aorta that result in increased sympathetic tone and vagal suppression. Initially, heart rate, cardiac contractility, and peripheral vascular resistance increase to compensate for the lower blood pressure. Additionally a number of circulating neurohumoral changes occur, including increased epinephrine and lower epinephrine/norepinephrine ratio that may further predispose to evolving hypotension. While controversial, some have proposed that when contraction of the left ventricle is enhanced (such as with prolonged upright posture or volume depletion), mechanoreceptors of the left ventricle are stimulated. This stimulation is transmitted to the brain stem (bulbar medullary nucleus) via C fibers, thus suppressing the vasomotor center and exciting the vagal center of the heart (Fig. 7.1) causing vasodilation and heart rate reduction via efferent fibers [4, 5].

7.2.1.3 Diagnosis

Vasovagal syncope is the most common type of syncope. Diagnosis is usually based on a careful history taking from the patient and witnesses. However, when VVS is suspected, but the history is inconclusive, a head-up tilt test is often performed.

The specificity of a head-up tilt test is approximately 90%; however, the sensitivity is only approximately 50% [4]. The reproducibility of a positive test is low, whereas a negative test shows a higher reproducibility. A VVS diagnosis is possible if syncope can be induced (particularly if it reproduces the patient's spontaneous symptoms), but VVS cannot be ruled out if syncope is not induced. In fact, the diagnosis is more often derived from the medical history. Therefore, it is important to understand the characteristics of VVS and obtain an accurate history.

The medical history is most important tool for the diagnosis of VVS. In brief, for patients with suspected syncope in the absence of any evident underlying heart disease, and occurring while the individual had been standing or sitting, and especially if accompanied by certain prodromes (e.g., pallor, hot/cold sensation, sweating, nausea), it is reasonable to suspect VVS. Similarly, if the patient is young, has no underlying heart disease, and faints during periods of stress (e.g., examinations, working overnight, working overtime, or irregular day-night rhythm) or after long periods of standing or sitting, then there is a high probability of VVS.

Clinical findings indicating VVS include the following: (1) a prodrome of abdominal discomfort, (2) nausea and sweating, (3) pallor, and (4) post-recovery fatigue.

As noted earlier, the head-up tilt test may help diagnose VVS when the history surrounding the episodes are not "classical" (i.e., the test is not needed if the story is classic). The indications for the head-up tilt test in the ACC/AHA/HRS [1] and the ESC guidelines [2] are similar.

7.2.1.4 VVS Treatment

Patient education and lifestyle modifications are essential elements in prevention of VVS recurrences. The avoidance of exacerbating factors, or as well as drug and non-drug treatments, may be appropriately combined depending on the frequency and severity of the attacks. Patients need to understand the condition and try to avoid triggering factors (e.g., dehydration, standing for a long time, drinking alcohol, etc.) as much as possible. In addition, physicians must instruct the patients to assume a supine or squatting position promptly when prodromes such as dizziness, nausea, and impaired vision (flashing lights, "grey-out" or darkening) occur. If patients are diagnosed with VVS and understand the condition, then mental stress decreases and patients can take action to avoid syncope such as physical counter-pressure maneuvers. In such circumstances, syncope recurrence may be reduced without medication. Nitrates, diuretics, alpha-blockers, or calcium antagonists should be reduced or discontinued if possible because they promote vasovagal syncope and reduce blood

pressure while standing. These modifications are a class IIb recommendation in the ACC/AHA/HRS [1] and a class IIa recommendation in the ESC guidelines [2].

For patients who continue to faint despite the avoidance of exacerbating factors, exhibit syncope of the cardioinhibitory type, and those with subtle prodromal symptoms, and those with sudden fainting that places them at high risk for trauma, pharmacotherapy should be considered as the first choice of treatment. See Chap. 23 for drug treatment of vasovagal syncope and Chap. 20 for pacemaker treatment.

The main difference between the two major practice guidelines is that midodrine treatment is considered a class IIa recommendation in the ACC/AHA/HRS guidelines [1], but it is considered a class IIb in the ESC guidelines [2] (Table 7.2). Beta-blocker treatment is a class IIb recommendation for patients older than 42 years according to the ACC/AHA/HRS guideline; however, it is class III according to the ESC guidelines. For cases of recurrent syncope for which spontaneous seizure-like activity has been confirmed on the electrocardiogram (ECG), the implantation of a dual-chamber pacemaker is a class IIb recommendation by the ACC/AHA/HRS [1] but a class IIa by the ESC guidelines [2] (Table 7.1). The argument is based on the presumption that abrupt cardioinhibition with rapid severe loss of brain perfusion must have been the cause.

Table 7.2 Treatment of reflex syncope

	2017 ACC/AHA/ HRS guidelines	2018 ESC guidelines
Treatment of reflex syncope	Class	Class
Education and lifestyle modifications	I	I
Discontinuation/reduction of hypotensive therapy	IIb	IIa
Encouraging increased salt and fluid intake	IIb	
Physical maneuvers	IIa	IIa
Tilt training	IIb	IIb
Fludrocortisone	IIb	IIb
Midodrine	IIa	IIb
Beta-adrenergic blocking drugs	IIb In patients aged 42 years or older	III
Selective serotonin reuptake inhibitor	IIb	
Cardiac pacing (in patients older than 40 years, with spontaneous documented symptomatic asystolic pause(s) >3 s or asymptomatic pause(s) > 6 s)	IIb	IIa
Cardiac pacing (in the absence of a documented cardioinhibitory reflex)		III
Permanent cardiac pacing (in patients with carotid sinus syndrome)	IIa Cardioinhibitory or mixed	IIa Cardioinhibitory carotid sinus syndrome Patients older than 40 years

This table is based on the 2017 ACC/AHA/HRS [1] and 2018 ESC guidelines [2]

7.2.2 *Carotid Sinus Syndrome*

7.2.2.1 Clinical Features

Carotid sinus syndrome is an infrequent cause of syncope that primarily occurs in older patients (mainly males) with unexplained fainting. Carotid sinus syndrome is more common in men and is often associated with coronary artery disease and hypertension [4]. See Chap. 14 for its pathophysiology and diagnosis.

Carotid sinus hypersensitivity refers to excessive sensitivity of the carotid sinus to manual massage (see the ESC guidelines for Methodology), but should not be considered to imply carotid sinus syndrome. Hypersensitivity has been observed in 39% of a random sample of patients older than 65 years; however, for patients with unexplained fainting, carotid sinus syndrome (i.e., hypersensitivity that reproduces the patient's symptoms of a faint) is far less often present [3, 4].

In carotid sinus syndrome, transient cerebral ischemic symptoms (e.g., light-headedness, fainting) are most likely to occur during standing, sitting, and walking, or with neck rotation such as when changing clothes, driving, lifting or lowering heavy objects, and with cervical pressure such as that caused by tight ties or collars. These symptoms may also be associated with cervical tumors (such as thyroid tumors), cervical lymphadenopathy compressing the carotid sinus, or after neck irradiation for malignancy. Carotid sinus syndrome should be considered as a cause of carotid sinus syndrome in individuals who have had prior neck surgery.

7.2.2.2 Treatment

Once again, patient education and lifestyle modifications are critical. In particular, patients should be taught to avoid the sudden cervical rotations and stretching that are assumed to compress the carotid sinus. There is a high risk of recurrence of symptoms and syncope if appropriate treatment is not performed. Repeated fainting associated with bradycardia, long cardiac pauses (probably >6 s), and trauma resulting from falls are generally accepted indications for pacemaker implantation.

Pacemaker treatment is recommended when repeated fainting is observed and carotid sinus stimulation demonstrates a cardioinhibitory mechanism. The ACC/AHA/HRS guidelines classify permanent pacemaker implantation for symptomatic carotid sinus syndrome as a class IIa recommendation for both the cardioinhibitory type and the mixed type [1]. The ESC guidelines classify pacemaker treatment for patients 40 years or older as a class IIa recommendation [2].

In the absence of symptoms, carotid sinus hypersensitivity of the cardioinhibitory type is not an indication for pacemaker treatment. However, since many of these patients are elderly and infirm, it may be difficult to concretely eliminate a connection between carotid sinus hypersensitivity and symptoms. With secondary carotid sinus syndrome due to a cervical mass that compresses the sinus, symptoms are likely to occur even when supine or sitting, and tumor resection is necessary.

7.2.3 *Situational Syncope*

7.2.3.1 Clinical Features and Pathophysiology

Situational syncope is, as its name suggests, triggered by certain evident actions, including micturition, defecation, swallowing, cough, breathing (Valsalva maneuver), and vomiting. These are forms of reflex syncope, and in each case the trigger may be different but the mechanism (as was the case with VVS) may be due to bradycardia or vasodepression or both. Each of the reflex pathways is shown in Fig. 7.1 [4]. The prognosis is generally dependent on the underlying disease, and it is important not to overlook serious underlying conditions. Elderly patients, in particular, often have cardiovascular abnormalities. The ACC/AHA/HRS [1] and the ESC guidelines [2] list examples of situational syncope but do not elaborate on the individual pathophysiology.

7.2.3.2 Micturition Syncope

Micturition syncope occurs more frequently in men who urinate in the standing position and is relatively common in middle-aged and older people; however, it also affects those in their 20s and 30s [10]. Susceptibility to micturition syncope may be greater immediately after urination when the person has been supine for a long period or lying in a warm bed at night before urinating [4]. Micturition syncope seems to be closely related to having been drinking alcohol recently (possibly due to the combination of volume and alcohol's diuretic effect) [4].

Micturition syncope occurs most often in young to middle-aged men [10]. It mostly occurs during the night (91% occur between 6 PM and 6 AM) [4]. People younger than 55 years often have fainting episodes while emptying the bladder after recently drinking alcohol, whereas persons 55 years or older often experience these episodes between midnight and the early morning hours [10].

The trigger for micturition syncope is not certain, but one pathophysiological explanation is that a full bladder may induce a hypertensive response that the baroreceptor system aims to modify. However, when the bladder is emptied rapidly, the hypertensive response vanishes, whereas the hypotensive reflex response is turned off only after a delay, resulting in transient hypotension [3]. This hypotension is aggravated by reduced peripheral vascular resistance because it occurs during the night or as an effect of alcohol, diuretics, or vasodilators [10].

7.2.3.3 Defecation Syncope

Defecation syncope is more common in women between ages 50 and 70 years and is often accompanied by gastrointestinal symptoms such as urgent defecation and abdominal pain [11, 12]. Many patients are asleep or are supine before defecation

syncope. Reports have indicated that defecation syncope often occurs during the night and until the early morning [4].

The mechanism of defecation syncope is believed to be multifactorial including: a decrease in peripheral vascular resistance in the supine position, decreased venous return because of defecation, and triggering of a vagal reflex through intestinal mechanoreceptors, resulting in decreased blood pressure, bradycardia, and cardiac slowing [13]. Elderly patients with defecation syncope often have underlying cardiovascular disease. Defecation syncope recurrences often occur.

7.2.3.4 Swallow (Deglutition) Syncope

Although swallow syncope is relatively rare, there are many case reports. The average age at the time of swallow syncope is 57 years (range, 15–85 years), and it is common among middle-aged and older patients. It has a higher incidence in men than women.

Swallow syncope is mainly caused by solid food, but it can also be triggered by carbonated drinks and hot or cold water. For patients with swallow syncope, bradycardia may also be induced by an esophageal balloon. Swallow syncope is frequently associated with esophageal disease, such as esophageal hernia, spasm, diverticulum, cancer, or achalasia [3]. Underlying heart disease is often found after myocardial infarction, especially inferior myocardial infarction [4]. Electrocardiographic monitoring often shows marked bradycardia, including asystole. This condition may overlap carotid sinus syndrome [3]. In fact, positive carotid sinus stimulation in swallow syncope patients has been reported [14].

Swallow syncope is believed to be caused by a vagal reflex due to an increased sensitivity of esophageal baroreceptors (Fig. 7.1). Although vomiting syncope has been reported, as with swallow syncope, it is thought to be caused by increased sensitivity of the baroreceptor to esophageal dilation [4, 5].

7.2.3.5 Cough Syncope

Cough syncope is more common in 30- to 50-year-old men, obese individuals, and those with a large thorax. These patients are prone to markedly increased intrathoracic pressure when coughing. Many of these patients are heavy smokers or have chronic obstructive pulmonary disease [4].

Cough syncope may be caused by either increased intrathoracic pressure or a vagal reflex. In the former, venous return decreases with increasing intrathoracic pressure, resulting in reduced cardiac output that adversely affects cerebral blood flow. Increased intrathoracic pressure further increases the cerebrospinal pressure and decreases cerebral blood flow by compressing the cerebral arteries. As a vagal reflex, it may be caused by baroreceptor hypersensitivity in the airways or carotid sinus [9].

7.2.3.6 Laugh (Gelastic) Syncope

Laugh (gelastic) syncope, also known as laughter-induced syncope, is a relatively rare subtype of situational syncope [15]. Our current understanding of gelastic syncope is derived from a few case reports. Cox et al. first reported an association between syncope and laughter in 1997. The exact mechanism is not well understood but is difficult to study due to its infrequency and unpredictability. During prolonged laughter, there is a repetitive Valsalva effect with increased intrathoracic pressure that reduces venous return and systemic arterial dilatation and bradycardia, ultimately resulting in reduced cardiac output and cerebral hypoperfusion. If the Valsalva maneuver is not aborted during the presyncopal phase, then it will likely culminate in syncope. This mechanism is similar to that seen with cough syncope [3, 16, 17].

7.2.3.7 Situational Syncope Diagnosis

The diagnosis of any of the situational syncope conditions depends upon obtaining a detailed medical history that establishes the circumstances surrounding the faint. Although a provocation test (e.g., coughing, swallowing, laughing) may be useful to confirm the diagnosis, it is often difficult to do and does not always reproduce the syncope.

With swallow syncope, bradycardia can often be reproducibly induced by swallowing solids or by use of esophageal balloons. Because cough syncope may be associated with carotid sinus hypersensitivity, carotid sinus massage is recommended for patients older than 50 years. Furthermore, Adkisson and Benditt [3] demonstrated that volitional cough induced more pronounced post-cough hypotension, reduced the chronotropic response to it, and prolonged its duration more in patients with cough syncope than in controls. The head-up tilt test is not very useful for situational syncope. However, cases of situational syncope are occasionally complicated by vasovagal syncope; therefore, the head-up tilt test may be performed in the absence of other more appropriate tests.

7.2.3.8 Situational Syncope Treatment

There is no established standard universal treatment for reflex syncope. Treatment is based on the individual medical condition. Situational syncope generally has a low frequency of attacks, and many patients are sufficiently managed with education and lifestyle modifications. Any patient with recognizable prodromes should be instructed to sit down or squat to avoid falls and shorten the event duration.

Patients with micturition syncope associated with alcohol should be advised to avoid excessive drinking and vasodilators. When drinking alcohol, patients, even males, should urinate in the sitting position. For patients with defecation syncope, physicians will prescribe treatment to prevent abdominal pain and diarrhea and

advise patients to avoid defecation at night if possible. Patients with swallow syncope are instructed to avoid swallowing large boluses of solids, and minimize drinking hot and cold water and carbonated beverages. When eating solids, patients should chew sufficiently before swallowing. Patients with cough syncope should quit smoking, and those who are obese should lose weight. Treatment of underlying pulmonary disease may be helpful to diminish cough susceptibility.

No drug therapy has been established for situational syncope although vasoconstrictors such as midodrine may be worth trying if medication is needed. Pacemaker treatment is indicated if education and lifestyle modifications fail to prevent syncope and if bradycardia or prolonged cardiac pauses are confirmed in association with syncope. Swallow syncope, in particular, often involves bradycardia and cardiac pauses, and pacemaker treatment is effective [3, 14]. For defecation syncope, monitoring has demonstrated marked bradycardia, and permanent relief after pacemaker implantation has been reported [13].

7.3 Conclusion

The prognosis of patients with reflex syncope is good. However, without intervention, patients are highly likely to continue fainting, resulting in anxiety, low quality of life, and increased injury risk. Therefore, it is important to make patients feel safe by establishing the diagnosis, and explaining it to both the patient and their family. To manage reflex syncope, physicians should conduct a thorough interview and explain the pathophysiology to patients. Treatment should be selected according to the severity of symptoms and aimed at improving patients' quality of life.

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Chapter 8

Orthostatic Hypotension Variants, POTS, and Less Well-Defined Autonomic Dysfunction



Artur Fedorowski

8.1 Introduction

In humans, the circulatory responses to postural changes involve complex adaptive mechanisms controlled by the autonomic nervous system [1]. After assuming an upright position, as the gravitational force displaces a substantial blood volume from thorax downwards, cardiovascular reflexes start acting to maintain both a stable blood pressure (BP) and adequate perfusion in the upper body. Orthostatic intolerance results from maladaptation of circulatory system to the effects of gravitational force in the upright and/or standing position [2]. Two main forms of orthostatic intolerance with distinct haemodynamic patterns are orthostatic hypotension (OH) and postural orthostatic tachycardia syndrome (POTS) [2, 3]. Orthostatic hypotension has three main variants defined by their temporal relationship to the act of assuming the standing position: initial (within 10–30 s after standing), classical (1–3 min after standing) and delayed OH (beyond 3 min of standing), the two latter characterized by persistent blood pressure (BP) fall [4, 5]. In POTS there is no BP fall on standing but excessive and continuous orthostatic tachycardia, usually accompanied by a spectrum of unspecific symptoms such as dizziness, discomfort, nausea, chest pain and palpitation [5–7]. Syncope is occasionally observed in OH and POTS; it may be provoked by sudden BP fall in initial OH, pronounced BP fall in severe classical OH, or by triggering the vasovagal reflex in both delayed OH and POTS [3, 4]. The overall prevalence of syncope in POTS is approximately 30% [6]. In general, European and American syncope guidelines are in agreement how to diagnose and manage the two most common syndromes of orthostatic intolerance.

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8.1.1 Orthostatic Hypotension

Orthostatic hypotension (OH) is a key manifestation of autonomic dysfunction, typically observed when cardiovascular adaptive mechanisms fail to compensate for the reduction in venous return that normally occurs on assuming the upright position [8]. It reflects a structural or functional sympathetic denervation, or a deranged reflex regulation of the sympathetic outflow [8, 9]. In some cases, blood pressure fall on standing may be due to volume depletion caused by insufficient fluid intake, dehydration caused by gastrointestinal, hormonal and renal disorders, or may be iatrogenic as a consequence of treatment with vasodilators and diuretics. This form of OH is potentially reversible in contrast to OH caused by chronic autonomic dysfunction [8]. Orthostatic hypotension frequently affects older people and patients who suffer from neurodegenerative and autoimmune diseases, diabetes, hypertension and renal failure.

In terms of incidence, OH is the second most common aetiology of syncope, occurring in approximately 15% of syncope presentations with a strong age-dependence; up to every third syncope in the age above 75 years may be attributed to this condition [4, 10]. Symptoms of OH may present as (A) an instantaneous short-lived BP fall while standing up, i.e., initial OH, or (B) persistent BP decrease during prolonged standing, with immediate (classical form, Fig. 8.1) or delayed and progressive BP fall (Fig. 8.2) [8]. The diagnostic criteria for different forms of OH are presented in Table 8.1. When the cerebral circulation becomes critically compromised by declining central arterial pressure, the susceptible individuals may complain of chronic fatigue, blurred vision, dizziness, a neck ache (“coat hanger distribution”) and, finally, fainting. In the delayed form of OH, the final loss of consciousness scenario may be similar to or identical with the vasovagal reflex, i.e., associated with bradycardia/asystole and signs of sympathetic activation.

The chronic symptoms of OH and risk of fainting with traumatic outcome affect especially older individuals who often are not aware of the problem or do not recognize the warning signs preceding the complete circulatory collapse. Consequently, detection and management of OH is crucial in order to improve the quality of life of affected patients, prevent syncopal attacks and fall-related injuries, as well as optimize treatment of concomitant diseases, such as hypertension, diabetes, heart and renal failure [8]. Unfortunately, OH is often unrecognized or misdiagnosed, and may be an overlooked factor associated with increased cardiovascular morbidity, fall tendency and all-cause mortality [8]. For the complete diagnosis of OH, cardiovascular (CV) autonomic testing is recommended, preferably with an access to a laboratory equipped with continuous beat-to-beat haemodynamic monitoring, tilt-table testing and trained staff [4]. The basic elements of CV autonomic workup are presented in Table 8.2. Management of OH is based on patient education, avoidance of triggers such as prolonged standing, dehydration, warm and humid environment, large meals and treatment with volume expanders and vasoconstrictors. However, pharmacological measures are not always satisfactory and may lead to complications such as supine hypertension [2]. The summary of interventions recommended for symptomatic OH can be found in Table 8.3.

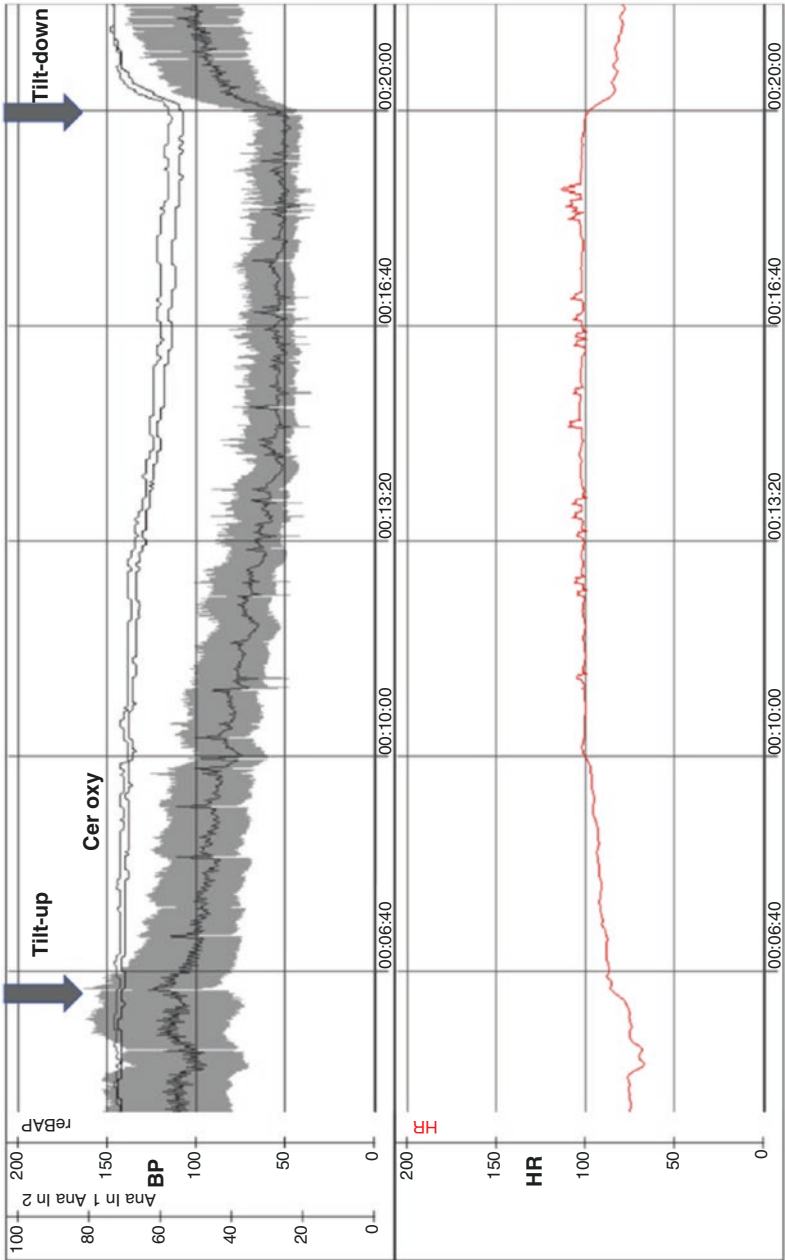


Fig. 8.1 Classical orthostatic hypotension. 50-year-old woman with unexplained syncope. Head-up tilt test demonstrates classical orthostatic hypotension with progressive decrease in blood pressure (BP) and cerebral tissue oximetry (cer oxy). Cerebral oximetry was non-invasively assessed using near-infrared spectroscopy. Patient faints when cerebral tissue oxygenation falls under 55% (tilt-down). *HR* heart rate

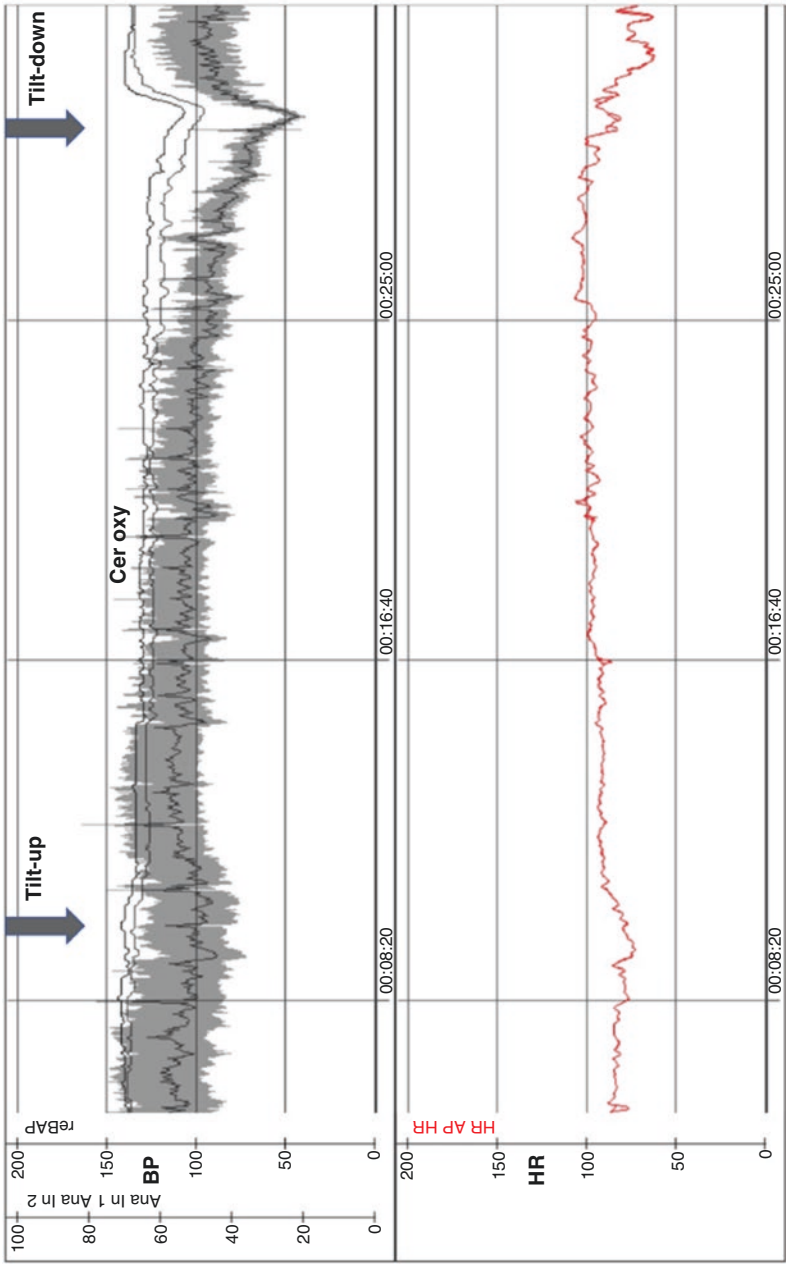


Fig. 8.2 Delayed orthostatic hypotension. 80-year-old man with unexplained syncope. Head-up tilt test demonstrates delayed orthostatic hypotension with progressive decline in blood pressure (BP) occurring first after 10 min of tilt testing. Cerebral tissue oximetry (cer oxy) non-invasively assessed using near-infrared spectroscopy declines significantly first after heart rate goes down, which implies vasovagal reflex component. Patient reports perspiration and dizziness before he faints when cerebral tissue oxygenation falls under 55% (tilt-down). *HR* heart rate

Table 8.1 The most common forms of orthostatic intolerance associated with syncope (adapted from: Brignole M et al. Practical Instructions for the 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J 2018; 39: e43–e80)

Orthostatic intolerance form	Ancillary test for diagnosis. Diagnostic criteria	Time from upright position to abnormal BP response	Pathophysiology	Most frequent symptoms	Most frequent associated conditions
Initial OH	Beat-to-beat BP on active standing test (lying/squatting to standing) BP fall > 40/20 mmHg	0–40 s	Transient mismatch between cardiac output, total peripheral resistance and sudden gravitational volume shift	Light-headedness, dizziness, visual disturbances a few seconds after standing up (syncope rare)	Young, asthenic subjects; old age, drug-induced (alpha-blockers)
Classical OH	HUT; Active standing test. BP fall > 20/10 mmHg or SBP < 90 mmHg (in hypertension: >30/15 mmHg)	<3 min	Impaired increase in total peripheral resistance and heart rate in autonomic failure resulting in pooling of blood; alternately, severe volume depletion	Dizziness, light-headedness fatigue, weakness, visual and hearing disturbances. Syncope may occur	Frailty, hypertension, diabetes, renal failure, drug-induced (any vasoactive drugs and diuretics), autonomic failure, hypovolemia
Delayed OH (optionally followed by reflex syncope)	HUT; Also active standing test. BP fall as above.	>3 min	Pathophysiology uncertain. Progressive fall in venous return and low cardiac output are likely	Prolonged prodromes (dizziness, fatigue, weakness, palpitations, visual and hearing disturbances, hyperhidrosis, neck or precordial pain) that may be followed by reflex syncope	As above. Autonomic failure of milder grade. Frequent comorbidities
<i>Orthostatic vasovagal syncope</i>	HUT; No OH/POTS	Usually prolonged standing	Vasovagal reflex due to progressive pooling of blood with final vasodepressive and/or cardioinhibitory pathways. Typical prodromes	Autonomic activation (nausea, pallor, sweating) precedes syncope	More common in women. Orthostatic VVS may be associated with chronic orthostatic intolerance

(continued)

Table 8.1 (continued)

Orthostatic intolerance form	Ancillary test for diagnosis. Diagnostic criteria	Time from upright position to abnormal BP response	Pathophysiology	Most frequent symptoms	Most frequent associated conditions
POTS	Active standing test; or HUT. HR increase>30 bpm (in age <18 years, increase >40 bpm) +symptoms of intolerance. No OH	<10 min	Debated; immune-mediated processes, excessive venous pooling and hyperadrenergic state advocated	Inappropriate HR increase without concomitant BP fall. Dizziness, deconditioning, headache, chest pain. Syncope is rare and usually elicited by vasovagal reflex activation	Young women overrepresented, recent infection or trauma, joint hypermobility syndrome

BP blood pressure (SBP systolic), HR heart rate, OH orthostatic hypotension, POTS postural orthostatic tachycardia syndrome, VVS vasovagal syncope, HUT head-up tilt-table test

Table 8.2 Diagnostic methods used for assessment of OH and POTS

Diagnostic test	Diagnostic outcome	Comment
Active standing test	Diagnostic criteria as presented in Table 8.1	Test may be used for initial screening and in clinics that lack access to fully equipped autonomic laboratory. Hypotension/tachycardia may be blunted by patient using muscle pump
Head-up tilt test with non-invasive beat-to-beat monitoring (Figs. 8.1, 8.2, and 8.3)	The characteristic haemodynamic pattern and reproduction of symptoms. (Table 8.1)	Head-up tilt test is a major component of CV autonomic testing [4, 9, 11, 12]
24 (48) -h ECG monitoring	Heart rate accelerations during daytime and in the morning after awakening. Normal heart rate night-time. Reduced heart rate variability	The test may be used to confirm the diagnosis and to discriminate POTS from inappropriate sinus tachycardia (elevated heart rate >90 bpm during 24 h and absence of typical night-time dip) [4, 7]
External or implantable loop recorders (ILRs)	ECG record of spontaneous fainting spells. Brady- or tachyarrhythmia. Epilepsy. Psychogenic pseudosyncope. Heart rate control	In very difficult diagnostic cases with multiple syncopal events, traumatic syncope, amnesia, therapy resistance, clinical suspicion of arrhythmia and epilepsy, this method might be recommended. Principally, it should be reserved for experts with good insights into syncope pathophysiology
24-h ambulatory BP monitoring	Hypertensive or hypotensive tendency. Low-BP phenotype. Circadian BP pattern (dipper, non-dipper, reversed dipper). White-coat hypertension	The results of BP monitoring may be used for tailoring the therapy with cardiovascular drugs [4, 8, 12]
Exercise ECG	The grade of overall physical performance and abnormal haemodynamic responses during exercise	This method may be used for quantification of remaining physical capacity and may play role in tailoring the physical therapy. It may also be recommended if patient faints during exercise
Echocardiography	Structural cardiac changes	Echocardiography is recommended for exclusion of possible underlying cardiac changes if physical findings and basic cardiac workup suggest presence of structural changes in the heart
Valsalva manoeuvre	Neurogenic (pathologic) Valsalva response suggesting autonomic denervation. Exaggerated BP and heart rate overshoot in phase IV suggestive of POTS	It may be used as a confirmatory test; it also suggests the presence of neurogenic OH or “hyperadrenergic” type of POTS [11]

(continued)

Table 8.2 (continued)

Diagnostic test	Diagnostic outcome	Comment
Laboratory tests	Anaemia, electrolyte disorders, thyroid disease, adrenal hormone abnormalities, elevated catecholamines and their metabolites in blood and urine (especially plasma norepinephrine during tilt testing)	These tests (except for catecholamines) should be considered in the basic workup for unexplained OH and postural tachycardia [3, 4, 13]
Non-cardiovascular autonomic function tests: gastrointestinal function tests, sudomotor function test, other autonomic tests, if available and appropriate	Autonomic neuropathy in different organs and body zones	These very specific tests should be performed in centres with sufficient expertise and access to appropriately equipped laboratories [13]. The positive results support the diagnosis of neurodegenerative disease with impact on autonomic nervous system [6]

Table 8.3 Therapeutic options for preventing symptoms of orthostatic intolerance (OH and POTS)

Therapy forms	Comments
<i>Non-pharmacological interventions</i>	
<p>Education of patient:</p> <ul style="list-style-type: none"> • Understanding of orthostatic intolerance pathophysiology (OH and POTS) • Avoidance of immobilization, prolonged recumbency and physical deconditioning • Gradual rising from supine and sitting position, especially in the morning, after meals and after urination/defecation • Small and frequent instead of large meals • Avoidance of prolonged standing, high ambient temperature and high humidity • Physical counter-manoeuvres (leg crossing, muscle tensing, squatting, etc.) during standing and prodromal symptoms [2] 	Education is the fundamental part of orthostatic intolerance management [3, 4, 7]. Patients and their families should understand the basics of orthostatic physiology and importance of non-pharmacological methods. Educational materials such as brochures, instruction films and links to the online education material may be very helpful
Exercise training	There are different programs available. A regular, structured, graduated and supervised exercise program featuring aerobic reconditioning with some resistance training for the thighs is preferable. Initial training should avoid upright position. Rowing machines, recumbent bicycles and swimming may be applied [7]

Table 8.3 (continued)

Therapy forms	Comments
<i>Non-pharmacological interventions</i>	
Increased salt and fluid intake incl. peroral water bolus if needed	Volume expansion. A daily dietary intake of more than 10 g of sodium per day or salt tablets (e.g., 1 g TID) and a fluid intake of at least 2 l per day is recommended. Hypertension, heart and kidney failure should be monitored [4, 7]
Compression stockings/garments	Reduction of peripheral pooling in the lower limbs and splanchnic region. In general, Class 2 compression garments (>30 mmHg) are recommended
<i>Pharmacological treatment</i>	
<i>Heart rate controlling agents (for POTS and IST)</i>	
Beta-blockers (propranolol, 10–40 mg TID; bisoprolol, 2.5–5 mg BID; metoprolol, 25–100 mg daily; atenolol, 12.5–50 mg daily)	Beta-blockers are especially recommended in “hyperadrenergic” POST subtype associated with sinus tachycardia >120 bpm on standing. Beta-blockers may aggravate orthostatic intolerance in low BP-phenotype, asthma and paroxysmal chest pain [2, 7]
Ivabradine (2.5–7.5 mg BID)	This drug is effective in low BP-phenotype [4] or when beta-blockers are not well tolerated
Verapamil (40–80 mg BID/TID)	This calcium channel blocker with negative chronotropic effect can be tested in “hyperadrenergic” POTS subtype associated with higher BP, migraine and chest pain
<i>Vasoconstrictors and volume-expanding agents (for OH and POTS)</i>	
Midodrine (2.5–10 mg TID)	Direct α 1-adrenoreceptor agonist. One of the few pharmacological agents positively tested in placebo-controlled studies for orthostatic hypotension [2, 4, 7]
Droxidopa (Northera, DOPS, 100–600 mg TID)	Peroral norepinephrine precursor. Drug has been empirically also used off-label in severe POTS and is recommended for neurogenic OH treatment in the USA [14]. Not included in the current European guidelines [2, 3]
Pyridostigmine (30–60 mg BID/TID)	Acetylcholinesterase inhibitor. It might be considered in OH and POTS-phenotype associated with autonomic neuropathy, gastrointestinal dysfunction and non-specific muscle weakness. Effect on BP is small
Fludrocortisone (0.1–0.2 mg daily)	Mineralocorticoid. Volume expander. Increases sodium reabsorption and enhances sensitivity of α -adrenoreceptors. May worsen supine hypertension and hypokalaemia
Ephedrine and pseudoephedrine (25/30–50/60 mg TID)	Direct and indirect α 1-adrenoreceptor agonist. Efficacy controversial [2]
Desmopressin (0.1–0.4 mg BID)	Vasopressin analogue. Volume expander. Increases water reabsorption and reduces nycturia. Efficacy uncertain
In-hospital acute 1–2 L physiological saline infusion (during consecutive 3–5 days)	In acute decompensated POTS (and possibly OH) this method could be considered to alleviate the short-term symptoms [3, 7]

BP blood pressure, *POTS* postural orthostatic tachycardia syndrome, *OH* orthostatic hypotension, *IST* inappropriate sinus tachycardia

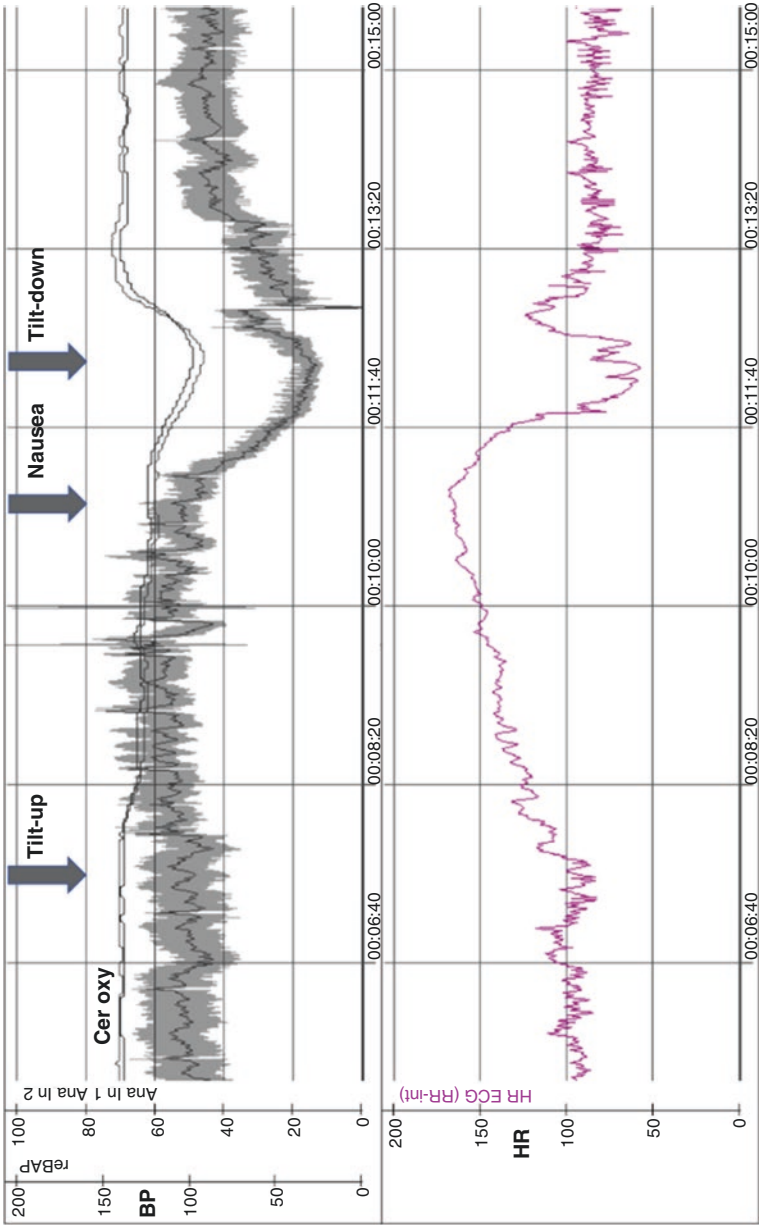


Fig. 8.3 Postural Orthostatic Tachycardia Syndrome. 17-year-old woman with symptoms of orthostatic intolerance and sporadic syncope. Head-up tilt test demonstrates postural orthostatic tachycardia syndrome with pronounced sinus tachycardia (165 bpm) and progressive decline in cerebral tissue oximetry (cer oxy) from 70% down to 60%. Cerebral oximetry was non-invasively assessed using near-infrared spectroscopy. Patient reports nausea before she faints when cerebral tissue oxygenation falls under 55% (tilt-down). Steep decline in BP and heart rate (HR) prior to syncope implies involvement of vasovagal reflex as the actual syncope mechanism

8.1.2 Postural Orthostatic Tachycardia Syndrome (POTS)

Postural orthostatic tachycardia syndrome (POTS) is a common variant of cardiovascular autonomic disorder characterized by an excessive heart rate increase on standing and orthostatic intolerance (Fig. 8.3). POTS is a condition affecting preferentially younger individuals 15–45 years old with a distinct female predominance ($\approx 80\%$). The estimated prevalence ranges between 0.2% and 1.0% in developed countries. The onset of POTS may be precipitated by immunological stressors such as viral infection, vaccination, trauma, pregnancy, surgery or psychosocial stress but its overrepresentation among patients with Ehlers-Danlos syndrome and chronic fatigue syndrome has been reported. The most common complaints are dizziness, weakness, rapid heartbeat and palpitation on standing. Moreover, patients often report physical deconditioning and reduced exercise capacity as well as headache, cognitive impairment, “brain fog”, dyspnoea, gastrointestinal disorders and diffuse musculoskeletal pain. The aetiology of POTS is largely unknown. Three main hypotheses have been forwarded including chronic autoimmune process, sympathetic hyperactivation and catecholamine excess, and peripheral sympathetic denervation leading to central hypovolemia and reflex tachycardia (Table 8.1). POTS is usually diagnosed by active standing test, which may be further confirmed and characterized using head-up tilt test with a non-invasive beat-to-beat haemodynamic monitoring (Fig. 8.3). Other tests that can be applied are 24-h ECG monitoring, for differential diagnosis with inappropriate sinus tachycardia, and exercise testing to assess the deconditioning grade (Table 8.2).

Although long-term prognosis of POTS is poorly understood; some patients spontaneously recover within 1–3 years but most are chronically affected with periods of exacerbation. After the diagnosis has been established, patient should be thoroughly educated about how POTS symptoms are generated, how to avoid triggers worsening orthostatic intolerance and what common measures may alleviate the symptoms. Exercise training may be very effective and counteract deconditioning. In more symptomatic patients, various drugs directed at controlling heart rate, increasing peripheral vasoconstriction and intravascular volume can be tested. However, the overall effects of pharmacological therapy are modest and the most affected patients remain handicapped.

8.1.3 Other Syndromes of Autonomic Dysfunction

In the presence of obvious disease of autonomic nervous system, OH may be classified as “neurogenic”, whereas in the absence of such condition, OH is “idiopathic”. Analogically, POTS may be classified as “primary” or “idiopathic” in the absence of disease that may cause postural tachycardia such as hyperthyroidism, pheochromocytoma or chronic deconditioning. When the aetiology of postural tachycardia is established, POTS may be classified as secondary.

Symptoms of orthostatic intolerance mimicking OH and POTS may be present in different conditions presenting with suspected autonomic nervous system dysfunction such as chronic fatigue syndrome, Mast Cell activation disorder, Ehlers-Danlos syndrome, orthostatic vasovagal syncope (see also: Table 8.1) and inappropriate sinus tachycardia (see also: Table 8.2) [7, 15]. Although difficult for an unexperienced clinician to discriminate, a detailed patient's history assisted by a battery of CV autonomic tests (Table 8.2) is usually capable of establishing the correct diagnosis although overlap may exist in up to one-third of OH and POTS patients [6, 15].

8.2 Conclusions

Orthostatic hypotension, among older patients, and postural orthostatic tachycardia syndrome, predominantly in young women, are the most common forms of cardiovascular autonomic dysfunction associated with occasional syncope. Diagnosis of OH and POTS can be established by patient's history, active standing test and cardiovascular autonomic testing; of these, tilt testing with continuous haemodynamic monitoring being the most accurate instrument. Both OH and POTS are associated with chronic orthostatic intolerance and less specific symptoms such as fatigue, head- and neck ache, as well as cognitive impairment. Treatment of these conditions should include correct diagnosis, patient's education, non-pharmacological measures such as trigger avoidance, increased fluid intake, compression garments and pharmacological agents such as volume expanders, vasoconstrictors and heart rate control in POTS.

Conflict of Interest Personal fees from Medtronic Inc. and Octopus Limedic AB.

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Chapter 9

Bradycardias and Tachycardias: Acquired and Inheritable



Matthew T. Bennett, Thomas M. Roston, Shubhayan Sanatani,
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9.1 Introduction

Many people will have at least one episode of syncope in their lifetime. The majority of these episodes of syncope are innocent and will not occur again. However, in certain instances, in particular when associated with primary brady- or tachyarrhythmias, syncope is more likely to be recurrent or predict risk of sudden death.

A comprehensive evaluation including patient history, physical examination, and directed investigations often allows the clinician to discriminate between innocent and sinister syncope. In this chapter we highlight the clinical features of the brady- and tachyarrhythmias that result in syncope. Identification of these features is the first step in risk stratification and directs the clinician to an optimal investigation strategy and, as such, timely diagnosis and treatment.

This chapter will complement Chap. 6 by describing the features that characterize arrhythmic syncope, and the recognition and management of the culprit arrhythmia. This will include a focus on the initial evaluation of the syncopal patient that distinguishes tachy- and bradyarrhythmias from the other forms of syncope and pseudosyncope described in Chaps. 6, 7, 8, and 10, outline an approach to interpretation of symptomatic and asymptomatic arrhythmias, and provide a limited overview of the nature and efficacy of related treatment strategies.

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9.2 Bradycardias and Tachycardias: Acquired and Inheritable

Arrhythmias account for approximately 14% of all causes of syncope [1]. As the prognosis of patients identified to have a cardiac cause of their syncope is significantly worse than those with other etiologies of syncope, a comprehensive understanding of the arrhythmias that cause syncope and their clinical features and associated conditions is essential; such an understanding will allow the clinician to identify which patients have syncope due to an arrhythmia and result in the most appropriate treatment.

9.2.1 *Clinical Features of Syncope Due to Arrhythmias*

We refer the reader to Chap. 5 which describes the initial evaluation of the patient with syncope. This evaluation will include a careful history and physical examination followed by directed diagnostic evaluation. The identification or exclusion of arrhythmias as a cause of syncope is essential as syncope secondary to arrhythmias carries a much worse prognosis than syncope secondary to other causes. Furthermore, this prognosis can be substantially improved with appropriate treatment.

Syncope secondary to primary arrhythmias (as opposed to reflex or drug-induced) is often preceded by no or a very short duration (<5 s) of symptoms. For example, syncope secondary to tachyarrhythmias may be preceded by a short duration of palpitations or no symptoms. In contrast, a long duration of irregular palpitations followed by syncope increases the probability of syncope due to a conversion pause. This is particularly likely in patients with a history of atrial arrhythmias who are in sinus rhythm/bradycardia immediately following syncope (e.g., patients in atrial fibrillation terminates abruptly followed by a pause).

Older patients or the presence of symptoms or a history of structural heart disease (heart failure, coronary artery disease, valvular heart disease, congenital heart disease, prior cardiac surgery) increases the likelihood of structural heart disease, ischemic heart disease or AV block and that the syncope is secondary to a primary arrhythmia. Typically, arrhythmic syncope occurs with little warning with immediate loss of consciousness and often with a quick return to normal function, i.e., minimal prodrome and postdrome. By contrast, autonomic activation (i.e., reflex syncope) with a prodrome of blurred vision, nausea, warmth, diaphoresis, or a long duration of regular palpitations with a description typical of sinus tachycardia before syncope/lightheadedness or a postdrome of nausea, warmth, diaphoresis, or fatigue is less likely to be associated with arrhythmia-induced syncope. An onlooker's report of the presence of blue tinged skin during a syncopal episode increases the probability of cardiac syncope compared to pallor which suggests reflex neurocardiogenic syncope. The presence of syncope during exercise and in particular swimming, or syncope that occurs while the patient is recumbent, should alert the clinician to an arrhythmic form of syncope. It is unusual for reflex neurocardiogenic syncope to occur while supine.

A comprehensive review of symptoms, past medical history, and medication review (prescription, non-prescription, herbal, and recreational) may also suggest an arrhythmic etiology of syncope.

To aid in identification or exclusion of an arrhythmic etiology of syncope, the physical examination should assess for the presence/absence of vascular disease and structural heart disease (the presence of volume overload, murmurs, ventricular enlargement).

Further investigation or empiric therapy will be dictated by the clinician's index of suspicion. This may include an assessment for structural heart disease (echocardiogram or MRI), ischemia (stress test, coronary CT, or angiogram), or long-term monitoring. In certain cases, empiric pacing or an ICD is preferred.

9.3 Bradyarrhythmias

Bradyarrhythmias account for 15–30% of all causes of syncope [2, 3]. Although cardioinhibitory vasovagal syncope results in syncope secondary to bradyarrhythmia, this will be described in Chap. 7 and, therefore, this chapter will focus on the remaining forms of bradyarrhythmias.

The mechanism of syncope attributed to bradyarrhythmias is a sudden drop in cardiac output due to a reduced frequency of ventricular contraction. In most instances, this is due to paroxysmal or persistent third-degree AV block or sinus arrest. In contrast, sinus bradycardia, first-degree AV block, and Mobitz I AV block present with no or mild symptoms and not typically with syncope. Although Mobitz II AV block alone does not usually result in syncope, it signifies advanced conduction system disease and a very high likelihood of progression to third-degree AV block (Fig. 9.1). Bradyarrhythmias can also result in syncope when associated with bradycardia-dependent QT prolongation and torsades de pointes.

9.4 Acquired Bradyarrhythmias

The most common causes of acquired bradyarrhythmias are caused by degenerative disease due to fibrosis within the cardiac conduction system or sinus node, iatrogenic causes secondary to AV nodal or funny current blockers, or conversion pauses in the patient with atrial tachyarrhythmias (Fig. 9.1). However, the clinician must consider many other less common causes such as infiltrative/invasive processes (sarcoidosis, amyloidosis, scleroderma, Chagas disease, rheumatoid nodules, cardiac tumors), inflammatory processes (polymyositis or myoendocarditis), myocardial infarction, electrolyte abnormalities, or direct injury at the time of catheter ablation or cardiac surgery.

Patients with atrial tachyarrhythmias, particularly those prescribed AV nodal blockers, which lengthen the sinus node recovery time, may have syncope secondary to conversion pauses immediately after spontaneous, medical or electrical cardioversion.

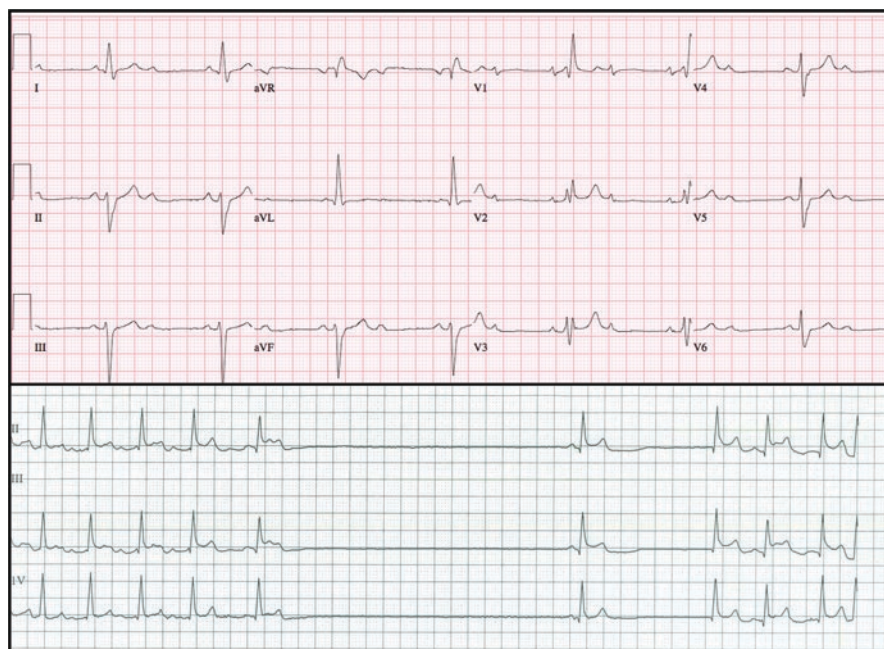


Fig. 9.1 Upper panel: 12 lead ECG from an 83-year-old woman with recent syncope with hip fracture. Previous ECGs showed sinus rhythm with right bundle branch block. The ECG now shows sinus rhythm with 2:1 conduction. Note the underlying right bundle branch block and left anterior hemiblock, concerning signs of recent or imminent third-degree AV block, a compelling indication for a permanent pacemaker. Lower panel: Rhythm strip in a 74-year-old male with a history of palpitations and syncope. Atrial fibrillation terminates with a 3.8 s pause, typical of sick sinus syndrome (also known as tachy-brady syndrome)

9.5 Inherited Bradyarrhythmias

The vast majority of intrinsic sinus node dysfunction and atrioventricular (AV) block in young patients are due to structural heart disease and related operative treatment. These patients are typically followed for known complex congenital heart disease (CHD). Presentation with syncope due to sinus node dysfunction or progressive conduction disease is uncommon, though patients with palliated complex heart disease have a high arrhythmia burden. Some forms of complex CHD are associated with a higher risk of bradycardia: congenitally corrected transposition, heterotaxy syndromes, and mitochondrial disease [4]. These are rare conditions that do not usually present with syncope.

Congenital complete atrioventricular (AV) block occurs in approximately 1 in 15,000 to 20,000 births and is usually due to the presence of maternal antibodies (Anti-Ro/SSA and Anti-La/SSB), which are directed at the developing fetal conduction system between 18 and 24 weeks gestation. These antibodies occur most commonly in women with Sjogren syndrome, systemic lupus erythematosus (SLE), and

other autoimmune conditions [5]. However, only one-third of women are symptomatic or have a known autoimmune condition.

Patients with congenital AV block are often diagnosed in utero with fetal heart rate monitoring. In those pregnancies known to be at risk, early surveillance including fetal echocardiography is recommended. However, the majority of patients are diagnosed with congenital complete heart block incidentally or following a syncopal event. Patients with syncope found to have complete heart block should be evaluated for reversible causes. This includes medication review and investigation for infection, notably myocarditis and Lyme disease, and other toxins [6]. Serologic testing of mothers of patients with congenital complete AV heart block can detect antibodies (anti-Ro and anti-La) even years after the gestation.

There is no data to determine whether congenital complete heart block that is diagnosed following a syncopal event infers causality, or whether this mandates the implantation of a pacemaker, as most patients with congenital complete heart block do not have an increased risk of syncope or cardiac arrest. The decision to implant a pacemaker will depend on the risk of recurrent syncope or cardiac arrest. This will be estimated through the history (symptoms consistent with arrhythmic or “Stokes-Adams” syncope vs. neurocardiogenic syncope) and in certain instances serial or prolonged rhythm monitoring. In addition, all patients with congenital complete heart block should have QT interval risk stratification to estimate the risk of bradycardia-induced QT prolongation and torsades de pointes [7].

There is an increasing number of genetic conditions associated with bradycardia (Table 9.1) [8]. These include mutations in the ion channels such as the hyperpolarization-activated cyclic nucleotide gated channels that contribute to the automaticity of the sinoatrial node (SAN). *SCN5A* encodes for the alpha unit of the cardiac sodium channel *NaV1.5*. Mutations are most known to be associated with long QT syndrome type 3 and Brugada syndrome, but have also been implicated in progressive cardiac conduction disease (PCCD), a familial degenerative disease of the conduction system. Mutations in the ryanodine receptor gene are identified in the majority of patients with catecholaminergic polymorphic ventricular tachycardia (CPVT). Interestingly, approximately one-quarter of CPVT patients also have sinus bradycardia. Syncope, however, is typically exertional or emotional stress related and due to ventricular tachycardia, not the baseline bradycardia. Mutations in the *Nkx2.5* gene are associated with structural heart disease, including septal defects, and AV block.

Genetic causes of sinus bradycardia or AV block can be considered particularly in younger patients where degenerative conduction system changes are less likely and when more than one family member is affected. Current family screening is limited to ECG assessment for all first-degree relatives when this is suspected.

The increase in the use of prolonged rhythm monitoring has allowed for the characterization of different mechanisms of bradycardia. Defining the mechanism is integral in risk stratification and the selection of appropriate treatment. Syncope associated with rapid and progressive slowing of the sinus rate over a several seconds or AV block associated with sinus slowing is consistent with neurocardiogenic

Table 9.1 Heritable bradyarrhythmias

Gene	Protein	Cardiac and other phenotypes	Pathophysiology of Bradycardia
<i>CASQ2</i>	Calsequestrin	Bradycardia, catecholaminergic polymorphic ventricular tachycardia, sudden death	Impaired Ca ²⁺ signalling
<i>PRKAG2</i>	5'-AMP-activated protein kinase subunit γ -2	Progressive conduction system disease, AV block, Wolff-Parkinson-White syndrome, sudden death	Glycogen accumulation in cardiomyocytes with decreased conduction velocity
<i>HCN4</i>	HCN	Bradycardia, noncompaction, ascending aorta dilation, atrial fibrillation	Reduced diastolic depolarization rate
<i>CACNA1G</i>	T-type Ca ²⁺ , Cav3.1	Bradycardia, neonatal lupus erythematosus	Reduced diastolic depolarization rate
<i>CACNA1D</i>	L-type Ca ²⁺ , Cav1.3	Bradycardia, deafness	Reduced diastolic depolarization rate
<i>SCN5A</i>	Nav1.5	Bradycardia, Brugada syndrome, atrial fibrillation, atrial flutter	SA node exit block and increased fibrosis with slowed action potential propagation
<i>TRPM4</i>	TRPM4	Bradycardia, Brugada syndrome	Change in membrane resting potential
<i>ANK2</i>	Ankyrin-B	Bradycardia, LQT4, atrial fibrillation, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia	Impaired localization and stabilization of ion channels, transport proteins, and Ca ²⁺ -handling proteins
<i>CAV3</i>	Caveolin-3	Bradycardia, LQT9, sudden infant death syndrome	Impaired localization of ion channels, transport proteins, and Ca ²⁺ -handling proteins
<i>RYR2</i>	RyR2	Resting bradycardia, catecholaminergic polymorphic ventricular tachycardia	Impaired Ca ²⁺ handling
<i>MYH6</i>	MYH6	Sick sinus syndrome	Impaired action potential propagation
<i>Nkx2-5</i>	Homeobox protein Nkx-2.5	Congenital heart diseases, progressive AV block	Defects in the development and functioning of the SA and AV nodes
<i>LMNA</i>	Lamins A and C	Bradycardia, AV block, several other laminopathies	–
<i>SGOL1</i>	Shugoshin-like 1	Chronic atrial and intestinal dysrhythmia	–

Table 9.1 (continued)

Gene	Protein	Cardiac and other phenotypes	Pathophysiology of Bradycardia
<i>TBX5</i>	T-box transcription factor TBX5	Progressive AV block, Holt-Oram syndrome, atrial septal defects	Aberrant gene transcription with abnormal conduction system development and decreased propagation velocities
<i>KCNJ2</i>	Kir2.1, inward rectifier K ⁺ -channel	AV block, bundle branch block, LQT7, sudden death, potassium-sensitive periodic paralysis, dysmorphic features	Prolongation of action potential
<i>HF-1b</i> (<i>SP-1</i> related)	N/A	AV block, sudden death	–
<i>GJA5</i>	Connexin 40/Gap junction α -5 protein	Cardiac conduction system abnormalities	Decreased conduction velocity from inhibited impulse propagation via gap junctions
<i>STA/EMD</i>	Emerin	AV block, sudden death, Emery-Dreifuss muscular dystrophy	Nuclear fragility and altered gene regulation/protein interactions leading to premature cell death
<i>DMPK</i>	Myotonic dystrophy protein kinase	AV block, sudden death	Expansion of unstable CTG trinucleotide repeats in 3' untranslated region with altered gene transcription

syncope. By contrast, AV block associated with an increase in sinus rate, often caused by AV node/His/Purkinje disease, and abrupt sinus arrest are often recurrent and irreversible and warrant the insertion of a permanent pacemaker.

9.6 Tachyarrhythmias

Tachyarrhythmias result in a substantial reduction in cardiac output due to a reduction in ventricular filling time. Transient hypotension is most common at the onset of tachyarrhythmias prior to the reflex activation of carotid baroreceptors that leads to vasoconstriction and blood pressure recovery. In most instances, syncope occurs at ventricular rates >200 bpm. However, in the presence of other comorbidities (reduced blood volume, decreased ventricular ejection fraction, mitral or aortic stenosis or pulmonary embolism), lower ventricular rates can result in syncope.

Tachyarrhythmias account for 5–13% [2, 3] of all causes of syncope. The most common tachyarrhythmias that cause syncope are either ventricular tachycardia (VT) or non-sustained ventricular fibrillation. In some instances supra-ventricular arrhythmias can cause syncope in conjunction with other hemodynamically

significant conditions (anemia, aortic stenosis, pulmonary embolism, reduced ejection fraction, etc.). An additional mechanism by which tachyarrhythmias result in syncope is at the termination of supra-ventricular arrhythmias (usually atrial fibrillation or atrial flutter). This results in syncope due to conversion pauses and a prolonged sinus node recovery time.

9.7 Monomorphic and Polymorphic VT

The monomorphic VT that results in syncope is usually scar-mediated reentry. In contrast, fascicular VT and outflow tract VT less frequently cause syncope, particularly as these forms of VT are less likely to be associated with structural heart disease. The most common causes of scar-mediated reentry are prior myocardial infarction due to ischemic heart disease or idiopathic/dilated cardiomyopathy. Although there may be other potentiating factors, in most instances the amount of scar correlates with the risk of developing ventricular arrhythmia in patients with cardiomyopathies. Acquired polymorphic VT is most often caused by myocardial ischemia, QT prolongation due to I_{Kr} blocking medications or bradycardia-dependent QT prolongation.

9.8 Inherited Arrhythmia Syndromes

The inherited arrhythmia syndromes (IAS), also known as cardiac ion “channelopathies,” are a group of genetically mediated disorders characterized by ventricular arrhythmias, syncope, and sudden cardiac arrest (SCA) (Table 9.2). While rare, it is important to consider IAS in patients presenting with syncope as they are a leading cause of sudden unexpected death (SUD) in young people without evidence of overt structural heart disease. 20–40% of patients found to have an inherited arrhythmia syndrome following a cardiac arrest had previously had syncope [9]. The most well-recognized forms of channelopathy are caused by mutations in the Na^+ , K^+ , and Ca^{2+} ion channel genes, leading to abnormal myocardial depolarization and/or repolarization. These include, but are not limited to long QT syndrome (LQTS), Brugada syndrome (BrS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) or more rare conditions, such as short QT syndrome (SQTS) and early repolarization syndrome (ERS).

9.9 Long QT Syndrome

Congenital LQTS is the most common cardiac ion channelopathy and affects approximately 1:2,000 people. Although the initial description of LQTS by Jervell and Lange-Nielsen was of sensorineural hearing loss and LQTS, later found to be

Table 9.2 Most frequent inherited arrhythmias syndromes

	LQT1	LQT2	LQT3	BrS	CPVT
Most common gene and electrophysiologic impact	KCNQ1 reduced IKs	KCNH2 reduced IKr	SCN5A increased INa	SCN5A (30% of cases) decreased INa	RyR2 (70% of cases) Ca ²⁺ leak from sarcoplasmic reticulum
ECG manifestations	Broad T wave with QT lengthening during exercise	Flat, notched T waves without significant QT interval change during exercise	Flat ST segment and short T wave duration	Type 1 Pattern: Coved (diagnostic) with ≥ 2 mm ST elevation in right precordial lead(s) Type 2 pattern: saddle back (non-diagnostic in isolation) with ≥ 0.5 mm ST elevation in right precordial lead(s)	Sinus bradycardia with progressive ventricular ectopy during exercise, typically beginning at 100–110 bpm
Approximate proportion of LQTS	40%	30%	15%	N/A	N/A
Specific triggers	Exercise, swimming	Post-partum, sudden loud noise, awakening or emotion. Increased female severity.	Sleep, wakeful rest. Increased male severity.	Sleep after heavy meal or alcohol, wakeful rest, febrile illness. Increased in males. Often occurs under high vagal tone.	Exercise, swimming, and heightened emotion
Beta-blocker efficacy	High	Partial	Partial	Ineffective	Partial
Secondary anti-arrhythmic options	LCSD	LCSD, mexiletine	LCSD, mexiletine, flecainide	Quinidine	LCSD, flecainide
Genotype-specific primary prevention ICD indications	None	QTc > 500 ms	QTc > 500 ms	None	None

associated with biallelic K^+ channel gene mutations, the majority of LQTS patients have heterozygous mutations and manifest a milder, but still life-threatening, isolated arrhythmic phenotype.

A diagnosis of LQTS is primarily suspected after unexplained arrhythmic symptoms in a young patient, and resting and stress ECGs showing QTc interval prolongation and/or T-U wave abnormalities without an alternative explanation (Fig. 9.2), at times coupled with a suggestive family history. These manifestations are either due to an impairment of repolarization or enhancement of depolarization current related to Na^+ , K^+ , or Ca^{2+} channel loss or gain of function. Among the >17 known genetic forms of LQTS, three predominate, each with its unique phenotypic manifestations including triggers for syncope [10]. For LQT1, gain-of-function mutations in *KCNQ1*, encoding $K_{V7.1}$ K^+ channel, predispose to adrenergic-related or swimming-related events. In LQT2, caused by *KCNH2*-encoded $K_{V11.1}$ K^+ channel mutations, the arrhythmic triggers are often sudden awakening, strong emotion or loud noises, and the post-partum period in women. Conversely, in LQT3, related to *SCN5A*-encoded $Na_{V1.5}$ Na^+ channel gain-of-function mutations, most events occur at rest or during sleep. The other forms of LQTS are very rare (<5% of all LQTS combined), while 10–15% of patients are genetically elusive despite extensive testing [10].

Since QT interval prolongation is a common and often acquired trait, the modified Schwartz Score is a standard set of criteria used to determine the probability of congenital LQTS [10]. Despite early data showing that LQTS posed a high risk of syncope and sudden death, systematic family screening and genetic testing have revealed that up to 1 in 3 LQTS patients has a normal QTc interval at rest, most patients require minimal treatment and, depending on the genotype, only 20–40% of patients will have any symptoms over their lifetime [10, 11]. Beta-blockade (preferably nadolol or propranolol) is recommended in most patients with LQTS, although asymptomatic individuals with a QTc interval of ≤ 470 ms may be able to forgo pharmacotherapy altogether [10]. Strict avoidance of electrolyte disturbances (in particular hypokalemia and hypomagnesemia) and QT-prolonging medications are cornerstones of prevention for all LQTS patients. Contraindicated drugs can be found at www.crediblemeds.org or through the associated smartphone app. Rarely, additional anti-arrhythmic drugs or procedures, like a left cardiac sympathetic denervation (LCSD) or an implantable cardioverter defibrillator (ICD), are required, and genotype helps to guide these decisions [10]. In this regard, several risk markers are predictive of worse outcomes, including a prior history of syncope, being a proband, having a high-risk genotype (autosomal recessive, or LQT2/LQT3), and/or expressing a very long QT interval (generally >500–520 ms) [10–12]. In general, guidelines recommend ICDs following a resuscitated cardiac arrest, after syncope despite beta-blocker or in patients with a high-risk genotype with a very long QT interval [10]. In certain circumstances, an LCSD and/or a Na^+ channel blocker may facilitate avoidance of an ICD.

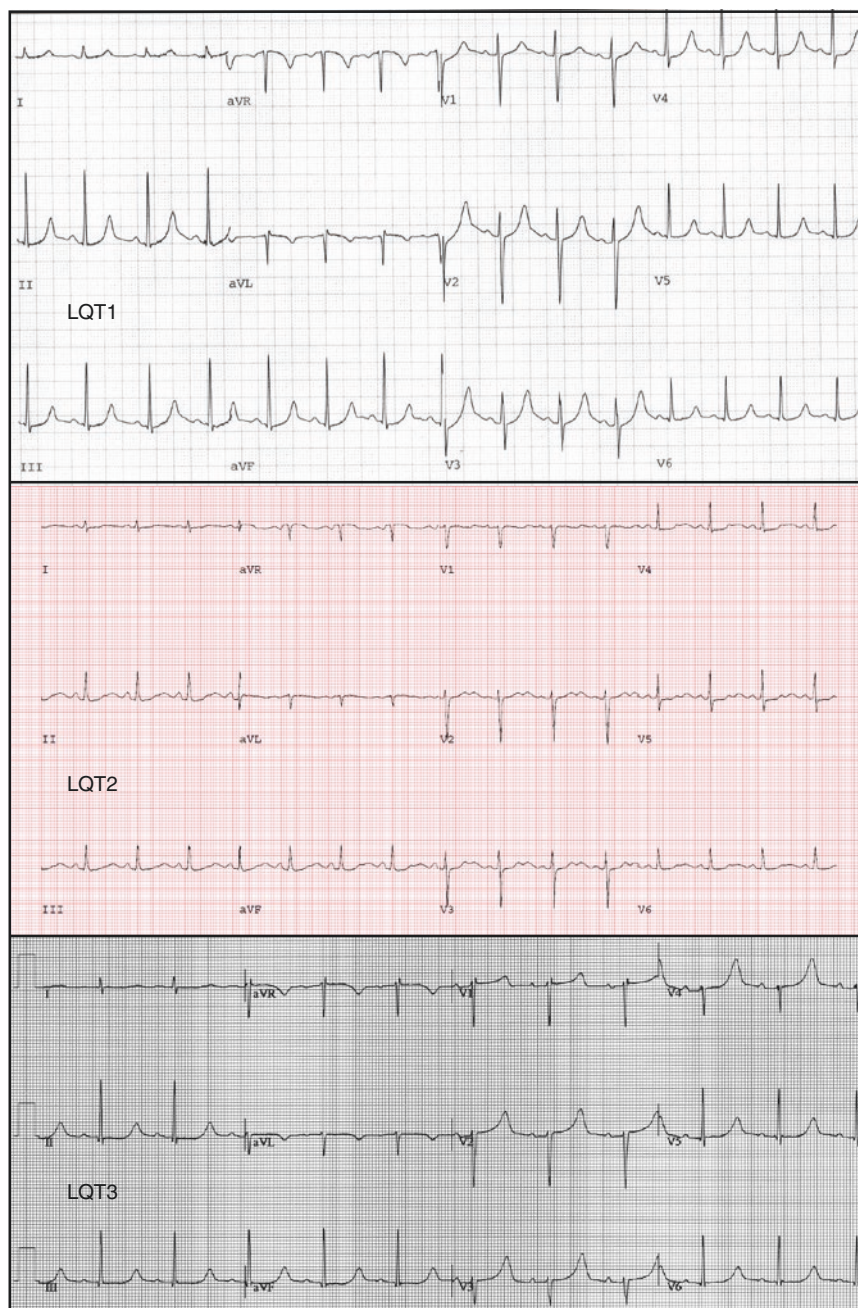


Fig. 9.2 Upper panel: 12 lead ECG from a young woman with Long QT type 1. Note the broad T wave. Middle panel: 12 lead ECG from a 27-year-old male with supine syncope during a heated argument. The low amplitude T wave with prominent humps and notching are classic for type 2 Long QT. Lower panel: 12 lead ECG from a 17-year-old male with nocturnal “spells” mistaken for seizures, with a family history of nocturnal sudden death. The long isoelectric segment followed by a delayed albeit normal morphology T wave is typical of Long QT 3

9.10 Brugada Syndrome

Brugada syndrome (BrS) is a rare, incompletely understood condition where abnormal Na^+ current dynamics predispose to right precordial lead ST elevation, syncope and SCA. Recent evidence suggests this may reflect a local epicardial cardiomyopathy in some patients. Two forms of ECGs patterns are described, and the addition of symptoms with a type 1 pattern constitutes Brugada syndrome. There are two types of Brugada pattern ECG changes: type 1 “saddle back” ECG and the type 2 “coved” ECG, both requiring at least 2 mm of ST elevation in V1 or V2 to qualify (Fig. 9.3) [10]. Previously, a “Type 3” pattern (unexplained ST elevation not meeting criteria for Type 1 or 2) was considered in the diagnostic criteria, but has since been abandoned due to a lack of specificity and relative frequency in the general population. The mechanism of BrS remains debated with both abnormalities of depolarization

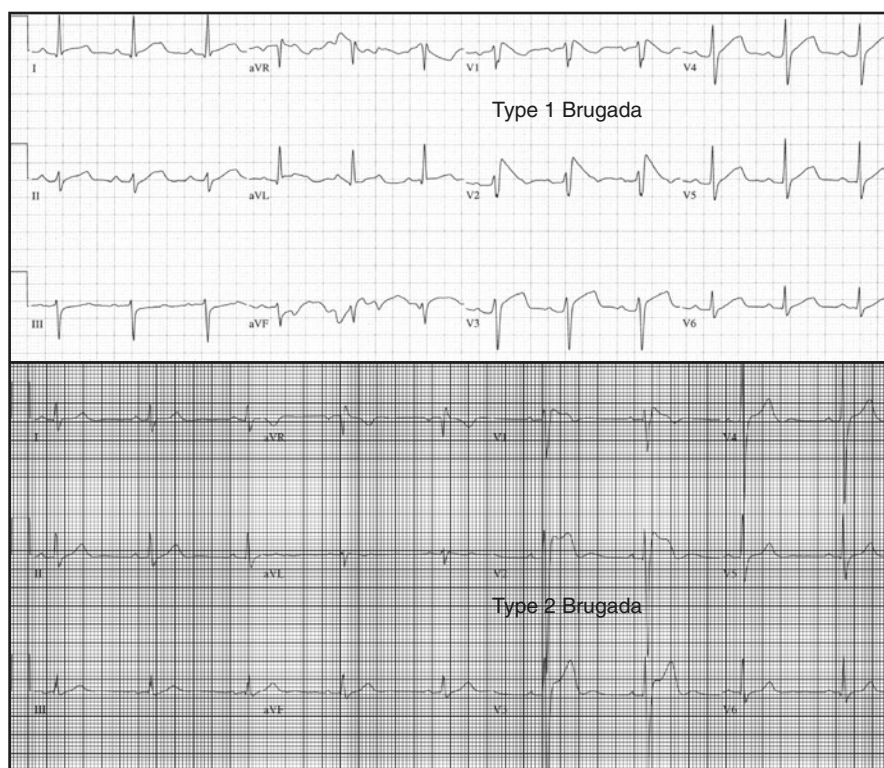


Fig. 9.3 Upper panel: 12 lead ECG from a 32-year-old male with a febrile “seizure” that was clearly syncope based on the account of an observer. Typical anterior precordial dome shaped ST elevation is diagnostic of type 1 Brugada pattern. The combination of ECG findings and symptoms leads to ICD implantation. Lower panel: 12 lead ECG from a 17-year-old Asian male with atypical chest pain shows the saddle back type 2 Brugada pattern. Inquiry into previous syncope, seizures, or family history of sudden death was negative

and repolarization being implicated. While the phenotype can be variable, there is an increased risk of BrS events in patients with fever, recent heavy alcohol use, and pharmacologic sodium channel blocker. The only well-established genetic cause of BrS is *SCN5A* loss of function mutations, with emerging data showing that all previous genes linked to BrS are of unclear significance [13].

A range of diagnostic criteria exist for BrS, with the “Shanghai Criteria” being the most contemporary consensus scoring system [14]. Another clinical challenge is that the Brugada pattern can be intermittent, meaning that a symptomatic BrS patient may have a normal resting ECG. Several factors can improve the sensitivity of the ECG in identifying a Brugada pattern. This includes using high precordial leads, which better position the precordial leads over the RVOT, or by concurrent intravenous sodium channel blocker infusion [10]. Despite a multitude of studies, including several large multi-national registries, the predictors of SCA in BrS are conflicting and poorly defined, with the exception of prior syncope. The utility of invasive electrical programmed stimulation to risk-stratify asymptomatic patients remains unclear.

At present, ICDs are recommended for patients with a history of SCA or arrhythmic syncope. Quinidine may be considered for patients with BrS and recurrent ICD shocks or in patients who refuse or have contraindications to an ICD. All patients with BrS or a Brugada ECG pattern should treat febrile illnesses early with antipyretic measures and avoid provocative drugs (www.BrugadaDrugs.org). There is promising emerging data to suggest that epicardial ablation may resolve the Type 1 BrS pattern and ameliorate arrhythmic risk.

9.11 Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT is a rare channelopathy (1:10,000) that leads to polymorphic or bidirectional ventricular arrhythmias and atrial arrhythmias during exertion or emotional stress. Almost all cases of CPVT are attributed to gain-of-function mutations in the cardiac ryanodine receptor (*RYR2*) gene [15]. Classically, CPVT is regarded as the most severe of the channelopathies, with a median age of symptom onset of 10 years and a very high risk of syncope or cardiac arrest at presentation (20–30%) [16].

The resting ECG is usually normal in CPVT, although lower resting heart rates are common. The diagnosis is made using stress ECG, which provokes a classic escalating pattern of initially bidirectional/polymorphic premature ventricular complexes (PVC) at a heart rate around 100–120 bpm, to more complex arrhythmias, including VT, with further exertion [10].

The cornerstones of therapy are a beta-blocker (preferably nadolol) and avoidance of adrenergic triggers (exercise and heightened emotion). Flecainide and LCSD are effective ancillary treatments for those with breakthrough arrhythmias despite beta-blocker. Because of the high burden of SCA in CPVT, an ICD is often recommended. In some pediatric CPVT populations the ICD implant rate exceeds 50% [16].

However, observational data have shown that ICDs are associated with exceedingly poor outcomes in CPVT, including inappropriate shocks for atrial arrhythmias, and appropriate shocks for stable VT that trigger faster and more unstable forms of polymorphic VT/VF [17]. As such, the role ICDs in CPVT remains controversial.

9.12 Other Forms of Inherited Arrhythmia

Other less common cited causes of IAS exist, including the very rare short QT syndrome, early repolarization syndrome (ERS), and idiopathic ventricular fibrillation (IVF). The latter are typically diagnosed in the setting of a sudden cardiac arrest, and are less commonly identified in isolated syncope. In an otherwise healthy individual, early repolarization pattern is usually of no consequence and requires no follow-up or intervention. Similarly, as VF rarely spontaneously resolves, the first arrhythmic symptom of patients with ERS and IVF is usually cardiac arrest and not syncope.

9.13 Screening for Inherited Arrhythmias

As syncope is common, a positive family history of syncope is also common and may not increase the probability of an inherited arrhythmia syndrome. A detailed family history is often elicited when a patient with syncope is found to have other features suggestive of inherited brady- or tachyarrhythmias or inherited cardiomyopathies. In younger patients with symptoms typical of arrhythmia-induced syncope, inherited arrhythmia syndromes must be considered, particularly when a family history of early sudden death are present. The evaluation for these conditions will include evaluation for structural heart disease to screen for ARVC, an exercise stress test and possible epinephrine infusion to evaluate QT dynamics and for catecholaminergic polymorphic VT and a sodium channel blocker challenge to evaluate for Brugada-type ECG changes. The yield of genetic testing varies depending on the condition and is not high enough to be diagnostic. Genetic testing is often used as a confirmatory test and to allow for family screening when positive.

Family screening is most often offered to all first-degree family members with further family screening dependent on results of the initial screened members. Family screening is usually performed after the proband has had all screening and based on these results.

9.14 Conclusion

Cardiac syncope typically presents with minimal prodrome and prompt recovery, and has a concerning natural history unless a cause is identified. A comprehensive evaluation including patient history, physical examination, and directed investigations allows the clinician to discriminate between innocent and sinister syncope.

Cardiac monitoring and evaluation for underlying structural and genetic causes typically leads to precise therapies of arrhythmic syncope based on the underlying diagnosis.

Conflict of Interest None

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Chapter 10

Differential Diagnosis of Autonomic Disturbances and Recognition by History and Physical Findings



Martina Rafanelli and Andrea Ungar

10.1 Introduction

The autonomic nervous system (ANS), through sympathetic, parasympathetic, and enteric components, both central and peripheral, maintains physiological homeostasis in health. Proper functioning of the ANS requires that both afferent and efferent limbs are intact. Afferent neurons detect changes in blood pressure (BP), temperature, and the myriad of other vital processes controlled by the ANS, and communicate these changes centrally, whereas the efferent neurons engage effector systems to perturb or restore homeostasis.

Several diseases such as primary neurodegenerative conditions [Multiple System Atrophy (MSA), Pure Autonomic Failure (PAF), Lewy Body Disorders (LBD), Parkinson Disease (PD)] may affect the widespread connections of ANS, but autonomic neuropathy may also be the manifestation of secondary processes, such as diabetic neuropathy, amyloidosis, and malignancies. Table 10.1 summarizes the different causes of autonomic failure (AF) [1]. In essence, autonomic dysfunction may result in impairment of cardiovascular, thermoregulatory, gastrointestinal, urogenital, sudomotor, and pupillomotor functions in different combinations and degrees of severity. Organ involvement in AF is listed in Table 10.2. The present chapter reviews the various clinical presentations of autonomic dysfunction, focusing on aspects of the clinical history and physical findings, which might help in the differential diagnosis.

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Table 10.1 Causes of autonomic failure, adapted from Bennaroch E.E [1]

<i>Isolated autonomic failure</i>	
1. Acute or subacute	
(a) Autoimmune autonomic ganglionopathy	
(b) Paraneoplastic autonomic neuropathy	
2. Progressive	
(a) Pure Autonomic Failure	

<i>Progressive autonomic failure associated with Parkinsonism, ataxia, or dementia</i>	
1. Multiple System Atrophy	
2. Lewy body disorders	
(a) Parkinson disease	
(b) Dementia with Lewy bodies	
3. Others	
(a) Familial leukoencephalopathies	
(b) Prion disorders	

<i>Autonomic failure associated with peripheral neuropathy</i>	
1. Chronic sensorimotor neuropathies	
(a) Diabetes	
(b) Amyloidosis	
(c) Other metabolic disorders (vitamin B ₁₂ deficiency, uremia)	
(d) Toxic neuropathies	
2. Sensory ganglionopathies	
(a) Sjögren syndrome	
(b) Paraneoplastic	
3. Distal painful neuropathies	
(a) Diabetes	
(b) Amyloidosis	
(c) Idiopathic (sodium channelopathies)	
(d) Infectious (HIV)	
(e) Hereditary	
1. Hereditary sensory and autonomic neuropathy	
2. Fabry disease	
3. Sodium channelopathies	
4. Acute or subacute motor polyradiculopathy or neuropathy	
(a) Guillain–Barré syndrome	
(b) Porphyria	
5. Acute autonomic and sensory neuropathy	
6 Ross syndrome (segmental anhidrosis, Adie pupils, and areflexia).	

10.2 Clinical Presentation

Autonomic disorders manifest with autonomic failure or hyperactivity, which may be generalized or focal. Disorders causing AF can be classified according to the presence or absence of associated neurological manifestations, such as peripheral neuropathy or Parkinsonism, and their temporal profile, which may be either acute, subacute, or chronic. The temporal evolution of autonomic disturbances has important implications in guiding the diagnostic pathway, Fig. 10.1 [1].

An acute or subacute onset of isolated AF suggests an immune cause such as autoimmune autonomic ganglionopathy (AAG), including post-infective or

Table 10.2 Organ involvement in autonomic failure

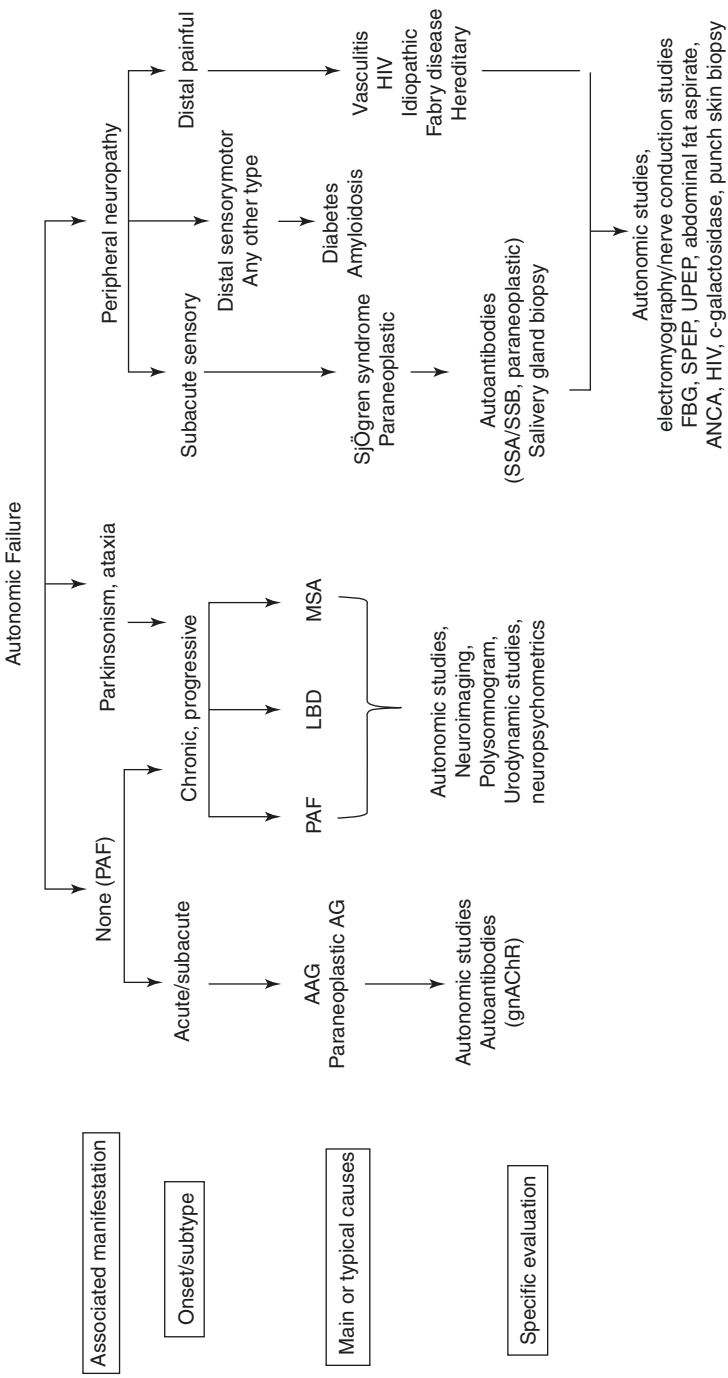
<i>Neurologic</i> Subtle neurologic signs (incoordination, rigidity) hyperreflexia	<i>Cardiac</i> Left ventricular hypertrophy Hypertensive heart disease
<i>Cardiovascular autonomic</i> Orthostatic hypotension Syncope Postprandial hypotension Supine hypertension	<i>Extremities</i> Venous pooling Acral color changes
<i>Sleep</i> REM sleep behavior disorder	<i>Thermoregulation</i> Anhidrosis Compensatory hyperhidrosis
<i>Gastrointestinal</i> Constipation Obstipation	<i>Urinary/sexual</i> Urgency, frequency Nocturia Urinary retention/incontinence Sexual dysfunction Impotence

paraneoplastic autonomic neuropathy. A slow development of generalized AF, without any motor or sensory symptoms, points to PAF. A chronic and progressive generalized autonomic failure coupled with ataxia or Parkinsonism suggests a degenerative cause, typically a synucleinopathy. Figure 10.2 shows a clinical classification of primary chronic autonomic failure syndromes.

Orthostatic hypotension (OH) is the main feature of cardiovascular autonomic failure in clinically established MSA, being the manifestation of impaired sympathetically mediated vasoconstriction of skeletal muscle and mesenteric vessels in response to baroreceptor unloading due to orthostatic stress. OH may also be associated with Parkinsonism, be drug-related, or be the first manifestation of malignancy or anemia; OH represents a frequent cause of syncope, especially in the older patient.

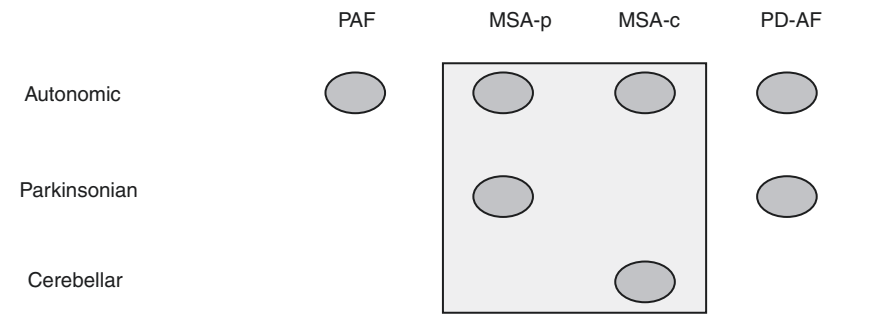
About one-half of the patients with neurogenic OH develop neurogenic supine hypertension, which is defined as systolic BP of ≥ 140 mmHg and/or diastolic BP of ≥ 90 mmHg, measured after at least 5 min of rest in the supine position. A loss of the physiological nocturnal BP fall at night of $\geq 10\%$ while supine and asleep may also be present, named as nocturnal hypertension. Patients are mostly asymptomatic or complain of headache and often exacerbation of pressure natriuresis during sleep, causing nocturia, sleep disturbances, volume depletion overnight and worsening of the BP fall upon standing in the morning [2].

The sympathetic nervous system mediates sweating through cholinergic activation of muscarinic M3 receptors in the eccrine sweat glands, contributing to an important thermoregulatory activity. Anhidrosis in autonomic failure may reflect impairment at different levels, central or peripheral, and depending on its distribution and severity, might be asymptomatic or manifest with hyperhidrosis in unaffected areas or heat intolerance [3].



PAF = pure autonomic failure, AAG = autoimmune autonomic ganglionopathy, LBD = Lewy Body Disorders, MSA = Multiple System Atrophy, AG = autonomic ganglionopathy, gnAChR = ganglionic nicotinic acetylcholine receptor, FBG = fasting blood glucose, SPEP = serum protein electrophoresis, UPEP = urine protein electrophoresis, ANCA = antineutrophil cytoplasmic antibodies.

Fig. 10.1 How to distinguish between causes of autonomic failure, adapted from Benarroch EE [1]



PAF = Pure Autonomic Failure, MSA-p = Multiple System Atrophy parkinsonian, MSA-c = Multiple System Atrophy cerebeller, PD-AF = Parkinson Disease with autonomic failure

Fig. 10.2 Clinical classification of primary chronic autonomic failure

The enteric nervous system, modulated by vagal and paravertebral sympathetic inputs, controls gastrointestinal motility. Dysphagia and regurgitation are manifestation of delayed esophageal transit. Delayed gastric emptying produces early satiety, anorexia, nausea, postprandial vomiting, and pain. Lower gastrointestinal dysmotility manifests with constipation and/or diarrhea [4].

Impaired micturition can result from lesions affecting afferents to the bladder, sacral parasympathetic neurons or their axons, or cholinergic muscarinic neurotransmission. Neurogenic bladder can manifest with detrusor hyperactivity, leading to urinary urgency with or without incontinence, urinary frequency, and nocturia. Detrusor underactivity is responsible for incomplete bladder emptying, urinary retention, and overflow incontinence. Neurogenic bladder may be associated with erectile and ejaculatory dysfunction in men and poor vaginal lubrication in women [5].

Patients with Lewy Body Disorders (LBD) may present with impaired odor identification, due to deposition of Lewy bodies in the olfactory bulb together with the anterior olfactory nucleus. This clinical manifestation may help separating LBD from MSA patients; the latter tend to have preserved olfaction [6].

10.3 Neurodegenerative Autonomic Failure Syndromes

10.3.1 Multisystem Atrophy (MSA)

Multiple System Atrophy or multisystem atrophy is an adult-onset, neurodegenerative disorder of presumed sporadic origin, morphologically characterized by Papp–Lantos bodies cytoplasmic inclusions, made of misfolded alpha-synuclein, which is normally located in neuronal axons and synapses [7]. MSA clinical features are represented by AF and motor impairment with variable combinations of poorly levodopa–responsive Parkinsonism, cerebellar ataxia, and corticospinal tract

dysfunction, differentiating the disease into two subtypes: [1] a Parkinsonian variant reflecting underlying striatonigral degeneration, MSA-p and [2] a cerebellar variant associated with olivopontocerebellar atrophy, MSA-c.

Orthostatic hypotension appears early in the disease, depends on the involvement of preganglionic sympathetic neurons and sympatho-excitatory neurons of the rostral ventrolateral medulla. OH is the main feature of cardiovascular autonomic failure in clinically established MSA, defined as a BP decrease of 30 mmHg systolic or 15 mmHg diastolic within 3 min of passive head-up tilt or standing from the recumbent position. Postprandial hypotension, supine and nocturnal hypertension are frequently associated with OH in MSA patients.

Even before cardiovascular AF manifestation, the disease may initially present with urogenital and sexual dysfunction, often misdiagnosed and attributed to other issues. The patient may suffer for urinary urgency, followed by incontinence and incomplete bladder emptying, due to a combination of detrusor hyperreflexia and urethral sphincter weakness followed by detrusor contraction failure [7].

MSA patients may also experience sleep-related breathing impairment, as sleep apnea and laryngeal stridor, due to impaired automatic ventilation and laryngeal dystonia with inspiratory adduction of the vocal cords, which are manifestations of brainstem neurodegeneration, with laryngeal muscle atrophy [8]. An inappropriate laughing or crying in the absence of the appropriate emotional context, depression, anxiety, panic attacks, and suicidal ideation may also be present. Cognitive impairment or decline, or visual hallucinations are rarer and should prompt consideration of dementia with Lewy bodies (LBD) [9]. A disabling pain is reported by the 50% of the patients [7].

10.3.2 Pure Autonomic Failure

Pure Autonomic Failure (PAF) is a rare, sporadic, adult-onset disorder related to degeneration of peripheral autonomic neurons along with alpha-synuclein inclusions, Lewy body-like, in sympathetic ganglia and widespread alpha-synuclein deposits in autonomic neurons.

The clinical expression of the disease is OH, which may be symptomatic or asymptomatic. Due to the slow progression of the disorder and the insidious onset, there may be a shift in the cerebral auto-regulatory curve, which leads to a proportion of patients tolerating a substantial drop in BP without symptoms. Patients may report dizziness, blurred or loss of vision, weakness, fatigue, and cognitive symptoms such as inattention. Occipito-cervical distribution pain may also indicate hypoperfusion of the neck muscles upon standing. Variable gastrointestinal, bladder and sexual dysfunction, without somatic motor deficits, may precede or accompany orthostatic hypotension.

Symptoms of PAF are less progressive and disabling than other neurodegenerative disorders. The diagnosis of PAF requires at least a 5 years history of isolated

autonomic dysfunction without other neurological manifestations, since after few years many patients with presumed PAF may develop cerebellar, extrapyramidal, or cognitive deficits indicating MSA, PD, or LBD [10].

10.3.3 *Parkinson's Disease (PD)*

Parkinson disease is mainly characterized by motor symptoms such as bradykinesia, rigidity, tremor, and postural instability. In addition, PD patients may also suffer from non-motor symptoms, as behavioral, sleep or perception dysfunctions as well as dysautonomia. This latter occurs more frequently with advances stages of the disease, and influences treatment and quality of life [11].

Dysautonomia is related to the almost ubiquitous loss of neurons and the appearance of Lewy bodies within completely different parts of the nervous system. Braak et al. [12] identified lesions in the dorsal vagal nucleus and in other autonomic cerebral stem centers within PD patients, before any clinical manifestation, as well as before the appearance of characteristic histopathological changes in the substantia nigra.

10.3.4 *Dementia with Lewy Bodies*

Dementia with Lewy Bodies (LBD) is classified as a synucleinopathy characterized by early development of progressive cognitive decline with cognitive fluctuation, visual hallucinations, and extrapyramidal Parkinsonian symptoms, which appear within approximately 1 year of each other. Dysautonomia is not required for diagnosis, but is a frequent supporting finding mainly represented by orthostatic hypotension, constipation, and urinary incontinence [13].

10.4 *Autonomic Peripheral Neuropathies*

Peripheral, postganglionic, disorders affect the neurons of the autonomic ganglia and the small lightly myelinated and unmyelinated autonomic nerve fibers extending to the target organs.

The temporal profile of autonomic peripheral neuropathy and its manifestations may be either acute, subacute for post-infective or paraneoplastic syndromes, or chronic for diabetes, alcoholism, and amyloidosis. Symptoms of autonomic dysfunction are either the only features or the predominant clinical features often masking the symptoms of somatic small fiber involvement [13].

10.4.1 Autoimmune Autonomic Ganglionopathy

Autoimmune autonomic ganglionopathy (AAG) includes a group of acquired disorders characterized by diffuse autonomic dysfunction with an immune-mediated pathophysiology and positivity of ganglionic nicotinic $\alpha 3$ -acetylcholine receptors autoantibodies. Frequently patients experience a viral upper respiratory tract or gastrointestinal infection, before manifesting the autonomic dysfunction. AAG may also be associated with vaccination, surgery, or interferon therapy.

Classically, AAG is a subacute disorder with monophasic onset, partial spontaneous improvement, and high antibody levels (>0.5 nmol/L, normal <0.05 nmol/L). However, some cases of slowly progressive autonomic dysfunction may actually represent limited forms of AAG and low antibody titers can be associated with the chronic form of autoimmune autonomic ganglionopathy. Patients with features of AAG, however, frequently have an associated malignancy, most of which are considered paraneoplastic syndromes [14].

10.4.2 Paraneoplastic Syndromes

Paraneoplastic neurological syndromes (PNS) are disorders of the nervous system occurring in association with a cancer, not related to any metabolic, infectious, degenerative, metastatic, or iatrogenic cause. PNS are thought to be secondary to an autoimmune reaction against neuronal antigens ectopically expressed by the underlying tumor. The most typical paraneoplastic neuropathy is the subacute sensory type, usually associated with small-cell lung cancer and anti-Hu antibody. When small myelinated and unmyelinated fibers loss is predominant, pain symptoms are mostly present, particularly mechanical hyperalgesia. Paraneoplastic syndromes may also manifest as autonomic dysfunction, predicting a worse prognosis, and are associated with paraneoplastic antibodies such as anti-Hu and anti CV2/CRMP-5. Symptoms of autonomic neuropathy may vary from OH, sicca syndrome, pupil involvement, urinary retention, sexual dysfunction, and gastrointestinal dysmotility. Paraneoplastic chronic gastrointestinal pseudo-obstruction is a rare condition, which may be associated with small-cell lung carcinoma, thymoma, gynecological, and breast cancer, and should be considered as part of the differential diagnosis in otherwise unexplained gastrointestinal motor dysfunction. The presence of autoantibodies against antigens shared by tumor cells and by enteric neurones (onconeural antigens, like anti-Hu, anti-VGCC, and anti-ganglionic acetylcholine receptors) has been hypothesized. Gastrointestinal symptoms usually precede tumor discovery, but not all cases have an underlying tumor [15].

10.5 Conclusions

The spectrum of clinical manifestations of autonomic disturbances is as wide as the myriad of vital processes controlled by the autonomic nervous system. A systematic clinical approach, a careful history and examination aimed at detecting different temporal profiles, evolvement of onset and associated neurological symptoms, may help differentiating among the major disorders.

Conflict of Interest The authors report no conflict of interest.

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Chapter 11

Psychogenic Pseudosyncope and Pseudoseizure: Approach and Treatment



Raffaello Furlan and Alessandra Alciati

11.1 Introduction

The 2018 Guidelines for the diagnosis and management of syncope of the European Society of Cardiology (ESC) [1] defined true Transient Loss of Consciousness (TLOC) as “a state of real or apparent loss of consciousness (LOC) with loss of awareness, characterized by amnesia for the period of unconsciousness, abnormal motor control, loss of responsiveness, and a short duration.”

Among non-syncopal forms of (real or apparent) TLOC, the ESC Guidelines described psychogenic “TLOC” which may occur in two forms, psychogenic pseudosyncope (PPS) and psychogenic nonepileptic seizures (PNES). In PPS, movements suggestive of seizure activity are absent, so the episode resembles a syncope, while PNES involves pronounced movements of limbs, head, and trunk, thereby resembling epileptic seizures (ES).

The purpose of this chapter is to provide an update regarding the diagnostic strategy and management of PPS/ PNES in adults based on guidelines, reviews, and relevant papers.

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Even though PPS and PNES share the same underlying psychiatric diagnosis of conversion disorder/functional neurologic symptom disorder (CD/FND), they have received different attention in the literature. As a result, PPS is relatively neglected. Moreover, the difference in clinical presentation generally affects how the patient is managed. Patients with PNES are likely to be referred to neurologists, while patients with PPS tend to be primarily referred to cardiologists, in search for a cause of the hypothesized syncope. For these reasons, in the present chapter, we choose to separately address PPS and PNES.

11.2 PPS and PNES History of Evolution of Thought

PPS and PNES are neurobehavioral conditions that can be placed at the interface of neurology and psychiatry, closely linked to the origins of medicine. Since being first described by the Egyptians in 1900 BCE and later framed as demonic possession with the rise of Christianity, PPS and PNES were introduced into the medical literature as “hysteria” in the nineteenth century. At the time the French neurologist Jean-Martin Charcot described a syndrome of “hysteria major,” the clinical picture of which was similar to PNES and theorized that the functional motor symptoms were due to a “dynamic lesion,” adversely impacting motor pathways. A reframing occurred through the writings of Sigmund Freud, the founder of psychoanalysis, who coined the term “conversion hysteria” to reflect the emergence of physical symptoms as an attempt to resolve, or to communicate, unconscious and unbearable psychic conflicts, often of sexual origin (psychic conflicts “converted” into physical symptoms).

The French psychologist Pierre Janet, Freud’s contemporary, theorized an important role for dissociation framed as a “retraction of the field of personal consciousness” in the psychological underpinnings of conversion disorder. By the late twentieth century, various and often contradictory concepts of dissociation were suggested. Currently, dissociation is used to describe a wide range of phenomena in which behavior, thoughts, and emotions may become separated one from another.

In the current medical nosology, the World Health Organization diagnostic system International Classification of Diseases ICD-10 places PPS/PNES under the category of dissociative disorders where the term *dissociative* implies compartmentalization or detachment of neurological functioning from the normal awareness. The fifth and last edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) included PPS/PNES in the Conversion Disorder (CD) (Functional Neurological Symptom Disorder, FND) under the category “Somatic symptoms and related disorders.”

11.3 Diagnostic Classification

For diagnosis, according to DSM-5 criteria, CD/FND must be characterized by the presence of one or more symptoms of altered voluntary or sensory function with clinical findings providing evidence of incompatibility between the symptom and

recognized neurological or medical conditions. The symptom or deficit must not be better explained by another medical or mental disorder and is expected to cause clinically significant distress or impairment in social and occupational activities that warrants medical evaluation. Of interest, the DSM-5 diagnosis of CD/FND does not require the judgment that the symptoms are not intentionally produced (i.e., not faked), as the definite absence of faking may not be a reliably discerned aspect. Conversely, in the context of definite evidence for faking, the diagnoses that should be instead considered would include factitious disorder or malingering.

Compared to the previous edition of DSM (DSM IV) diagnostic criteria, the DSM-5 diagnosis of CD/FND added the criterion of physical diagnostic features, removed the criteria requiring an association with psychological stressors and the exclusion of malingering or factitious disorder. These changes have made DSM-5 CD/FND diagnosis criteria more appropriate for research studies than for clinical use due to the potential for greater interrater reliability and compatibility with specialty-specific diagnoses, including PPS and PNES.

Alongside these diagnostic advances, the availability of brain functional imaging makes it possible to explore the neurobiological basis of conversion disorders. Brain imaging key aspects are as follows: First, there are clear brain activation patterns associated with CD/FND. They strongly support the concept that patients are not faking their symptoms. Second, the finding of a decreased activation of the right temporoparietal junction (TPJ), which plays a central role in integrating sensory inputs with expected actions, may account for the patient's loss of the feeling of acting, a symptom frequently reported after the attack. Third, the finding of a hyperactive amygdala and its heightened connectivity with motor circuitry may represent the underlying mechanism by which strong emotions may directly influence motor control. The increased knowledge of the clinical and neurobiological nature of the CD/FND resulted in a refinement of the diagnostic processes and therapeutic strategies.

11.4 Psychogenic Pseudosyncope (PPS)

From 2009 the European Society of Cardiology (ESC) Guidelines on syncope have defined TLOC as an “apparent loss of consciousness” with the word “apparent” explicitly added to allow the inclusion of PPS along with syncope, epileptic seizures, and other rare causes of disorders of the consciousness.

PPS is an apparent loss of consciousness in the absence of impaired cerebral perfusion or function. The prevalence of PPS in patients presenting for syncope evaluations has been reported to span from 0% to 12%, with a mean rate of 4%. This wide range of frequency may likely represent an underestimation, taking into account particular care settings such as the tertiary syncope clinics, where up to 20–30% of syncope episodes remain undiagnosed after an extensive evaluation and are defined as “unexplained syncope” (US).

A detailed history is central for the diagnosis of PPS and its differentiation from vasovagal syncope (VVS), the most frequent cause of syncope. In spite of its high frequency of onset, due to its *transient* nature, TLOC is rarely witnessed by

medically trained individuals. However, from the clinical standpoint an eyewitness account becomes crucial [1].

In order to obtain clinical recognition and to distinguish PPS from VVS, Tannemaat [2] analyzed 800 tilt-table tests. Interestingly enough, 43 patients (5.4%) were diagnosed as suffering from PPS. The median duration of apparent TLOC was longer in PPS (44 s) than in VVS (20 s) and, during the event, the eyes were closed in almost all PPS (97%) whereas in VVS in only 7%. A sudden head drop while moving down the tilt table was more common in PPS than in VVS, whereas jerking movements occurred more frequently in VVS. In a retrospective examination of the medical records of 1401 consecutive patients referred to a syncope unit [3], fourteen patients (1.0%) were diagnosed as having PPS and up to 50% of them presented with the initial diagnosis of VVS. Patients with PPS were characterized by a high frequency of attacks (53 ± 35 attacks) during the preceding year, whereas in most trials on VVS, the median number of syncopal events preceding the observation was 3–6 episodes per year. In addition, PPS showed prolonged loss of consciousness (minutes to >1 h) and a clinical history of former psychiatric disorders.

It is worth noting that an initial diagnosis of VVS does not exclude the subsequent diagnosis of PPS, as previously noted from the retrospective study of Saal et al. [4]. In that investigation, 57% of patients with the final diagnosis of PPS had also a preceding diagnosis of syncope. Compared with patients with pure VVS, patients with a combination of tilt-induced VVS and PPS, a pattern defined VVS/PPS, had higher attack frequency, delayed recovery of consciousness, apparent loss of consciousness >1 min, ictal eye closure, atypical triggers (exercise, or supine position in the absence of facilitating factors such as venepuncture or pain), and the absence of prodromes [5].

Literature results were summarized in the 2018 ESC Guidelines [1]. Among the specific characteristics of TLOC, highly suggestive of PPS and collectible by an appropriate history taking, there were the ictal eye closure, long duration of LOC, high frequency of attacks, and no recognizable triggers and prodromes. As relevant key features during an attack, 2018 ESC guidelines indicated sleep-like body position with closed eyes and lack of response to speech or touch, eyelid flicker, eyeball movements, swallowing, intact muscle tone, and resistance to eye-opening (see the video).

The 2017 American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society (ACC/AHA/HRS) Guideline for the Evaluation and Management of Patients with Syncope [6] stated that tilt-table testing (TTT) “is reasonable to establish a diagnosis of PPS.” PPS attacks occur at a variable interval after head-up tilt (generally within 1 or 2 min) and are associated with no decreases in blood pressure (BP) or significant changes in heart rate (HR). Usually both BP and HR increase few minutes before the PPS, reaching peak values during the attack [1]. This pattern remarkably differs from that of VVS, where at least BP or HR decreases, and more often both decline before syncope.

According to the 2018 ESC Guidelines, an easy and helpful way to diagnose PPS is the recording of an attack by a cell phone camera. Alternatively, a tilt test may be

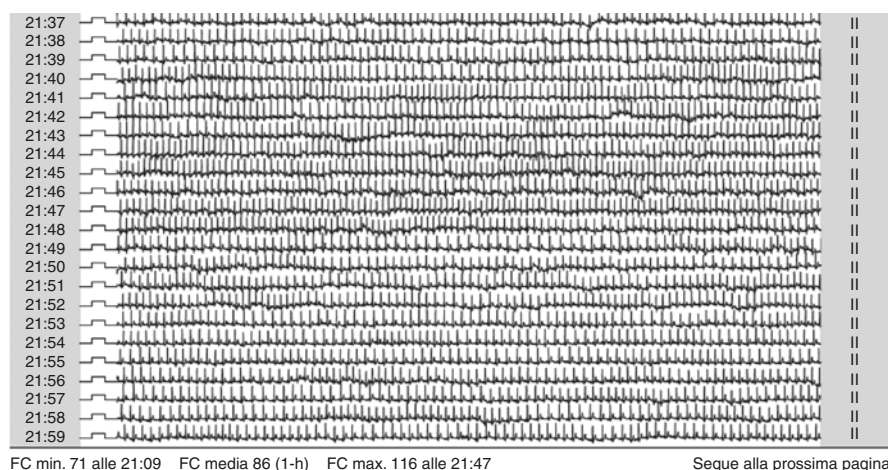


Fig. 11.1 ECG continuous recording by an external ECG loop recorder during an 18 min lasting PPS episode. Please notice the absence of any arrhythmia and abrupt change in RR interval which instead slowly fluctuated from 78 b/min up to a peak of 116 b/min at 9.47 pm (time: 21.47). These are crucial features differentiating PPS from vasovagal syncope. In the latter, RR interval may be found either reduced (i.e., heart rate (HR) is increased) in the case of a syncope vaso-inhibitory type or increased (i.e., reduced HR up to heart standstill) in the case of pure cardio-inhibitory or mixed syncope types. Every strip refers to a 6-s ECG recording. FC indicates HR, media indicates mean

used when suspecting PPS. As shown in Fig. 11.1, BP and HR values are within the normal ranges during a PPS attack prompted by a tilt-table test. When recorded, EEG was found to be normal during PPS. ACC/AHA/HRS 2017 guidelines suggest that simultaneous monitoring of EEG and hemodynamic parameters during a tilt-table test may be able to distinguish between syncope, pseudosyncope, and epilepsy when a diagnosis cannot be established after a thorough initial evaluation. Notably, during “true” syncope, the EEG may undergo characteristic features and stereotyped series of changes. Indeed, regardless of the type of syncope, i.e. vasovagal, cardiac, or hypotensive, EEG changes tend to reflect cerebral hypoperfusion. This latter includes a slowing of background rhythms, followed by high amplitude delta activity, mainly anteriorly. The documentation of patient’s unresponsiveness in the absence of abnormal slow electrical activity and in the presence of a normal alpha (α) rhythm of the brain suggests the psychogenic nature of the episode.

Clinical clues that should raise the suspicion for a psychogenic nature of the PPS may also help in differentiating PPS and VVS and are summarized in Table 11.1.

Of interest, there are only few organic coma-like states characterized by a normal EEG alpha rhythm, namely the locked-in syndrome and the persistent vegetative state. However, these clinical conditions are persistent (i.e., not transient such as syncope or PPS) and cannot be induced by placebo maneuvers. Notably, PPS events are amenable to suggestion and can be induced, among others, by tilt-table testing, induction techniques, or placebo maneuvers in the vast majority of the PPS patients.

Table 11.1 Hemodynamic and EEG parameters during tilt-table test (TTT)

	Hemodynamic parameters during TTT		EEG during TTT
	Blood pressure	Heart rate	Alpha rhythm
Vasovagal syncope (VVS)	Decreased	Decreased	Slowing
Psychogenic pseudosyncope (PPS)	Increased or normal	Slightly increased or normal	Normal

Table 11.2 PPS management and therapy

Guidelines	Recommendation	Class of recommendation	Level of evidence
2018 ESC Guideline [1]	Doctors who diagnose PPS should present the diagnosis of PPS to the patients CBT may be considered in the treatment of PPS if attacks persist after explanation	Ia Ib	C
2017 ACC/AHA/HRS Guideline [2]	In patients with suspected PPS, a candid discussion with the patient about the diagnosis may be reasonable CBT may be beneficial in patients with PPS	Ib Ib	C-LD (limited data) C-LD

Ia weight of evidence/opinion is in favor of usefulness/efficacy, *Ib* usefulness/efficacy is less well established by evidence/opinion, *C* consensus of opinion of the experts and/or small studies, retrospective studies, registries, *CBT* cognitive behavioral therapy

Presently, the long-term outcome of PPS is yet to be completely elucidated. A retrospective cohort study of 35 patients with PPS referred to a tertiary center for syncope revealed a reduction in the number of attacks, with one-third of patients who were attack-free at the follow-up of >4 years [4]. Importantly, conveying the diagnosis to the patient resulted in an immediate decrease in attacks in 1 month and a shift from somatic to mental health care. Unfortunately, the quality of life was still low for both attack-free patients and those who were still symptomatic, suggesting that the underlying psychopathology negatively impacts the quality of life more than the mere presence of PPS attacks.

Guidelines recommendations for management and therapy of PPS are summarized in Table 11.2

11.5 Psychogenic Nonepileptic Seizure (PNES)

PNES is a paroxysmal alteration of sensory and/or motor function that resembles epileptic seizure but does not show corresponding abnormalities in brain electrical activity. It may be the same as PPS but the motor activity is far more evident in PNES.

About 10–30% of patients presented to tertiary epilepsy centers for evaluation are diagnosed as having PNES. PNES is two to three times more common in women,

and its onset peaks in the third decade of life. PNES has been described in both developed and undeveloped countries with different clinical characteristics (likely due to different cultural, ethnic, and religious factors). Both epileptic seizures (ES) and PNES may occur in the same patients. The prevalence of coexisting ES/PNES has been estimated to span from 10% to 50%. Such a wide range of prevalence is likely related to the variability of criteria used for the diagnosis of either ES or PNES.

The precise diagnosis of ES, PNES, or their coexistence (ES/PNES) represents a clinical challenge with important treatment implications. The delay in diagnosis of PNES has been estimated to be about 8 years. During this period patients are often treated with antiepileptic drugs being thereby exposed to potential adverse drug side-effects. Among the later adverse effects that is of remarkable clinical importance is the possible teratogenic risk for women of childbearing age. Moreover, patients with ES/PNES can mistakenly be classified as drug-resistant epilepsy and treated with complex combinations of antiepileptic compounds or even referred to epilepsy surgery.

The reference test for the diagnosis of PNES is the Video-Electroencephalogram (VEEG). This latter should be recorded in the ictal phase. As this tool is available only in specialized centers and not all patients present with seizures while under VEEG monitoring, in daily clinical practice, diagnostic hypothesis is often made based on the information obtained from witnesses. As in the case of PPS, several studies have investigated the clinical signs that may help to diagnose PNES. The clinical features which may reliably distinguish PNES from ES include the long duration of the event, the fluctuating course, asynchronous or side-to-side head or body movements, pelvic thrusting, ictal eye closure, ictal crying, and postictal recall of information. Conversely, the occurrence in association with the “seizure” of EEG-verified sleep, postictal confusion, and postictal stertorous breathing all favor the diagnosis of ES. Of note, urinary incontinence and tongue biting do not reliably distinguish ES from PNES [7].

In 2011, a clinical practice consensus based on an international survey of experts carried out by the Commission on Neuropsychiatric Aspects of Epilepsy of the International League Against Epilepsy (ILAE) identified PNES as one of the ten key neuropsychiatric issues associated with epilepsy. Afterward, the ILAE Commission on Neuropsychobiology Nonepileptic Seizures Task Force was founded and charged with developing a consensus on minimal requirements for the diagnosis of nonepileptic events [8]. The following four diagnostic levels of certainty for PNES, based on a witnessed event, history and electroencephalogram (EEG) findings, have been proposed (see also Table 11.3):

11.5.1 Possible PNES

The diagnosis is based on minimum features that are available in the vast majority of clinical situations. They are: the patient’s history, description of events, an eye-witness description of the critical episode, a normal routine or sleep-deprived

Table 11.3 Elements featuring different likelihoods of PNES diagnosis

Diagnostic level	Clinical history	Witnessing	EEG
Possible	Event clinical features consistent with PNES	Patient, witness	Normal routine/sleep-deprived interictal EEG
Probable	Event clinical features consistent with PNES	Clinician's analysis of the semiology typical of PNES obtained by video or in person	Normal routine/sleep-deprived interictal EEG
Clinically established	Event clinical features consistent with PNES	Clinician experienced in the diagnosis of seizure disorders analyzing features and semiology typical of PNES obtained by a video or in-person	Normal EEG recordings during habitual events
Documented	Event clinical features consistent with PNES	Clinician experienced in the diagnosis of seizure disorders, in the presence of a clear previous clinical history and semiology of PNES, by analyzing features and semiology typical of PNES, in person or on video EEG	Normal video EEG recordings during habitual events

interictal EEG. Patient's description of the event can help to distinguish between PNES and ES. Patients with PNES tend to provide few details regarding the situations in which the episode has occurred or its consequences, while those with ES tend to readily give detailed accounts of subjective pre-seizure and seizure symptoms. In the absence of a witnessed event, including a recorded video and in presence of interictal epileptiform discharges (IEDs), an alternative diagnosis of epilepsy should be considered.

11.5.2 Probable PNES

The diagnosis of probable PNES is based on the clinical history, the presence of a doctor during the event, the clinician's review of a video recording of the episode all showing features and semiology typical of PNES (as described earlier) and normal interictal or sleep-deprived EEG recording.

11.5.3 Clinically Established PNES

A clinical diagnosis is made by an experienced doctor in seizure disorders, while witnessing in person the event or after observing a video of the attack, and by the analysis of an EEG recording characterized by absence of epileptiform activity during the event, in the presence of a clinical history and semiology typical for PNES.

11.5.4 Documented PNES

A documented diagnosis is made by a clinician experienced in seizure disorders and it is based on the presence of a *clinical history typical* of PNES, *semiology typical* of PNES as assessed directly by the physician, and a *video EEG* capturing a typical event, characterized by the absence of any epileptiform activity immediately before, during, or after the event.

11.6 Management of PPS/PNES

In 2013 the International League Against Epilepsy (ILAE) Neuropsychobiology Commission provided practical guidance for health professionals as to the pharmacological and non-pharmacological treatment of patients with PNES. In brief, the management of PNES comprises three different stages that are the diagnosis, the communication of the diagnosis, and the treatment [9]. Each of the stages is separately addressed, as follows.

11.6.1 The Diagnostic Process

A formal psychiatric assessment should be provided early in the diagnostic process with the purpose to rule out similar disorders, in particular panic attack, and to recognize and treat frequent psychiatric comorbidities. These latter may range from 53% to 100% and may affect the treatment. The meta-analysis by Diprose and colleagues [10] showed that depression was the most common comorbidity, ranging between 8.9% and 85%, while anxiety disorders (in particular panic disorder) rates ranged from 4.5% to 70%. The prevalence of post-traumatic stress disorder (PTSD) ranged even more widely, i.e. from 7% to 100%. Personality disorders rates were up to 74.3% from 5.4%. Patients with PNES had significantly higher rates of chronic pain disorders such as fibromyalgia, more severe form of migraine, and increased use of prescription pain relievers compared to patients with epilepsy. Moreover, patients with PNES showed a high rate of functional medical disorders, including irritable bowel syndrome and chronic fatigue.

About three-fourths of patients with PNES reported prior traumatic experiences, including sexual (~30%) and physical abuse (~25%). Finally, several studies described increased rates of adverse life events occurring close by the disease onset.

11.6.2 Communicating the Diagnosis

Reports suggest that patients may benefit from being informed clearly but empathetically of the diagnosis of PPS/PNES. In newly presenting video EEG-confirmed PPS/PNES, half of the patients were seizure-free at 3 months after the presentation

of diagnosis and interestingly enough in most of them, PNES ceased immediately after the communication. The communication of the diagnosis to the patient, relatives, or both, even several years after attack onset, seemed to have a greater short-term impact on healthcare utilization than on clinical seizure control. Indeed, a reduction of PNES-related use of emergency services up to 69% and of diagnostic test costs by 76% was observed. This was however achieved in the presence of unmodified rate of attacks. Interestingly, patients who ceased using emergency services did so immediately after the diagnosis, thus suggesting a specific therapeutic effect of the diagnosis communication [11].

It has to be pointed out that, although improvement as outlined above was the clinical evolution of the large majority of patients, a few patients showed an increase in PPS/PNES frequency as high as more than 50% from what recorded before the diagnosis. In these patients, diagnosis was also followed by an exacerbation of other concomitant psychiatric symptoms.

Several studies detailed the supposed optimal communication strategies for delivering the diagnosis of PPS/PNES. Within quite large differences, there seems to be agreement that PNES should be presented as a common and recognizable condition, independent of the patient's self-consciousness and control, frequently related to upsetting emotions most of which the patient could be completely unaware of. Patient and relative should be reassured that psychological interventions may help to reduce attack frequency, psychological distress and improve the quality of life [9]. Studies on the long-term outcome of PNES showed inconsistent results. Previous investigations showed that up to 25–29% of patients were found to be PNES-free after a mean follow-up of 5 years. In contrast, more recent investigations focused on a time frame of analysis of 5–10 years after diagnosis found that 68% of patients did not access any healthcare facility for possible seizures or related disorders continuously for 6 months. A recent long-term follow-up study revealed that more than half of the patients with untreated PNES were seizure-free during the past 12 months and that the longer the duration of PNES before they had definite diagnosis, the worse was their long-term outcome.

11.6.3 Treatment of PPS/PNES

Psychotherapy is currently viewed as the treatment of choice for PPS/PNES. Cognitive behavior therapy (CBT), which has been shown to be effective in the treatment of several somatoform disorders, is the psychological intervention supported by the most solid evidence. CBT combines cognitive therapy with behavior therapy by identifying faulty or maladaptive patterns of thinking, abnormal emotional response or behaviors, and substituting them with assumed desirable patterns.

The CBT approach to the treatment of PNES is based on a “fear avoidance” model. PNES is viewed as dissociative responses to cognitive, emotional, physiological, or environmental cues that patients tend to associate with previously intolerable or fearful experiences. Dissociative responses are maintained by the avoidance

of conditions that can trigger the attacks, as well as by several other behavioral, cognitive, affective, physiological, and social factors. This model of PNES maintenance supports the use of a series of standard CBT interventions, including graded exposure to avoided situations, treatment of mood disorder, and problem-solving techniques.

The first support to the potential efficacy of CBT in PNES has come from small uncontrolled studies and pilot randomized controlled trials (RCTs). In 2010 a pilot RCT provided evidence that, as compared to SMC alone, a structured CBT in addition to standard medical care (SMC) significantly reduced attack frequency in patients with PNES at the end of the 4-month treatment, with a tendency for this benefit to be maintained at the 6-month follow-up [12].

A second pilot, multi-center RCT [13] was designed to compare in patients with PNES (1) CBT informed psychotherapy (CBT-ip), by a 12-week lasting individual sessions targeting behaviors and cognitions (2) CBT-ip together with the antidepressant sertraline, (3) sertraline alone, and (4) treatment as usual (TAU). CBT-ip and the combined CBT-ip/sertraline groups reduced PNES attacks by 51.4% and 59%, respectively. CBT-ip group (without and with sertraline) also resulted in a reduction of depression and anxiety symptoms, with improved quality of life and global functioning. The sertraline-only group did not show a reduction in PNES attacks. The TAU group showed no significant PNES events reduction or improvement in psychiatric symptoms, quality of life and global functioning.

Individual or group psychotherapy with a psychodynamic focus and individual and group educational programs have been shown to be effective in reducing PPS/PNES attacks frequency and psychological distress in uncontrolled studies with a pre-post design. Of note, few of those studies were based on more than twenty participants. The goal of psychodynamic therapy was to facilitate awareness of physical manifestations of psychic processes and the role of childhood experiences in the development of maladaptive behavioral patterns.

A few longitudinal studies have investigated hypnosis, paradoxical intention therapy, and mixed psychological intervention. The vast majority of these studies reported improved outcomes for the intervention under investigation.

A Cochrane review [14] aimed to assess whether behavioral or psychological treatments for PNES might result in a reduction in the frequency of attacks or improvement in quality of life, or both, and whether a single treatment was more effective than the others. That review concluded that there was poor evidence supporting the use of a specific treatment, including CBT, in comparison with the others, as a therapeutic option for PPS/PNES.

The meta-analysis of Carlson and Nicholson Perry [15] examined the effectiveness of various types of psychological treatments for PNES (three studies of CBT interventions, four of psychodynamic treatment, one of paradoxical intention therapy, one of mindfulness-based intervention, two of psychoeducational intervention, and two of eclectic interventions) on two primary outcomes: attack reduction greater than 50% or more and PNES freedom. Overall, results showed that 47% of participants were PPS/PNES freedom and 82% had a reduction in the events frequency greater than 50% upon completion of psychological intervention. The results of

such meta-analysis are to some extent in contrast with data from existing literature showing that from 14 to 23% of patients who did not receive psychotherapy, a spontaneous reduction in seizure frequency of about 50% after 16-week [13] or 52-week [11] follow-up was reported.

The actual role of CBT in the treatment of PNES will be clarified by the CODES (COgnitive behavioral therapy vs standardized medical care for adults with Dissociative non-Epileptic Seizures) trial. CODES trial is the first properly powered, multicenter, randomized controlled trial (RCT) aimed to investigate the clinical effectiveness and cost-effectiveness of CBT plus standardized medical care (SMC) compared with SMC alone.

11.7 Conclusions

PPS and PNES are believed to be different clinical expressions of the same underlying psychiatric condition, i.e. the conversion disorder/ functional neurological symptom disorder CD/FND. Difference in symptoms affects the clinical setting in which the patient is diagnosed and managed. The recent guidelines agree that many patients with PPS/PNES can be diagnosed by a careful history addressing the presence of key clinical features such as high frequency of attacks, long duration of the event, and ictal eye closure.

When a diagnosis cannot be established after a thorough initial evaluation, simultaneous monitoring of an EEG and hemodynamic parameters during tilt-table testing in case of PPS and a video EEG in the case of PNES may offer a diagnostic “gold-standard” with high levels of certainty and excellent reliability. Notably, video-EEG may be of value also for PPS diagnosis.

PPS and PNES are frequently associated with earlier adverse events and to a vast array of other psychiatric comorbidities which need a formal psychiatric assessment and appropriate therapy if possible.

The treatment of PPS and PNES include a clear and empathic communication of the diagnosis to the patients, parents, and relatives. Information about the best-validated psychological approach should be promptly provided to the patients and family members.

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Part III

Basic Diagnostic Strategies

Chapter 12

Managing Syncope/Collapse in the Emergency Department



Matthew J. Reed

Syncope/collapse is a common reason for Emergency Department (ED) attendance. It can present a major challenge in terms of appropriate workup and disposition. Nearly 50% of patients are admitted to hospital, and for many this is unnecessary. In March 2018, the European Society of Cardiology (ESC) launched a new version of their guidelines for the diagnosis and management of syncope [1]. These syncope guidelines have multidisciplinary representation including for the first time, emergency medicine.

The guidelines have three main new focuses. Firstly, for the first time there is a section on the management of people presenting to the Emergency Department (ED) with syncope/collapse. This section describes how to diagnose syncope, rule out serious underlying diagnoses (both non-cardiovascular and cardiovascular), and if the cause of the patient's syncope/collapse remains undiagnosed, to risk stratify the patient according to the likely diagnosis. A patient likely to have a reflex or postural syncope will be at low risk of a serious outcome (although collapse in the elderly is associated with increased risk of adverse outcome). However, a patient likely to have cardiac syncope will be at high risk of a serious outcome. Management should then be based on the outcome of this risk assessment.

Previous ESC and NICE guidelines have attempted to aid the clinician in assessing the likely cause and risk, but the new guidance is the first to very specifically guide clinicians on which patients should be deemed high risk, while also attempting to reduce hospital admission rates with alternative investigative strategies (e.g., syncope assessment/decision units and rapid access syncope clinics). The second focus

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of the new guidelines is to advocate the syncope clinical decision unit, including clear recommendations as to how it should be set up. Finally, the guidelines recommend an enhanced role for prolonged ECG monitoring in patients with unexplained falls, suspected epilepsy, and recurrent severe unexplained syncope.

12.1 Has My Patient Had Syncope?

The term “syncope” must be carefully applied. It is one of two main causes of transient loss of consciousness (TLoC). The other commonest cause for this is epileptic seizure. Differentiating the two is not always straightforward. The 2018 ESC guidelines highlight the difficulty of diagnosing TLoC as being of syncopal origin (i.e., due to cerebral hypoperfusion) in the ED [1]. The SYNcope Expert Research Group International (SYNERGI) [2] suggests a pragmatic definition of syncope: “a transient loss of consciousness, associated with inability to maintain postural tone and with immediate spontaneous and complete recovery” [3]. A very careful history is needed to differentiate syncope from epilepsy and other non-TLoC conditions such as presyncope, lightheadedness, vertigo, disequilibrium, and accidental or mechanical collapse (i.e., loss of postural tone).

In the absence of witnesses, information from the patient regarding prodrome, provocation, and prior history can be useful; information from witnesses, particularly on the time to recovery will be extremely helpful (as this is a key factor to differentiate syncope from seizure). Where paramedics are involved, examine the ambulance notes for initial observations and review any prehospital ECGs. These are a great source of useful information that can be hard to locate later down the line and copies should be made when first seen. In most cases clinicians can establish whether the presenting problem was syncope, and therefore TLoC patients should not be labeled as “collapse query cause.” This implies a lack of attention to the history of the event and leads to poor patient management, treatment, and disposition decisions.

12.2 How Should I Approach the Patient with Syncope?

Firstly, the diagnosis of syncope should be established with some thought given to the ranking of likelihood of various causes. Secondly, any serious underlying diagnoses, both non-cardiac (e.g., pulmonary embolism, ruptured abdominal aortic aneurysm) and cardiac (e.g., complete heart block on presenting ECG) should be sought. If the cause of the patient's syncope/collapse remains undiagnosed, then risk stratification of the patient should take place according to likely diagnosis. History is key (including witness history) and examination should include focused cardiovascular examination.

12.3 Risk Assessment

The new ESC guidelines are very clear on risk assessment if the patient's syncope remains undiagnosed after initial assessment. Risk assessment is designed to decide whether a patient is likely to have reflex or postural syncope (low risk of serious outcome) or cardiac syncope (high risk of serious outcome). The guidelines provide a list of high- and low-risk features that can be used for ED risk stratification [1]. These are summarized below:

Syncopal Event

Low risk:

- Associated with prodrome typical of reflex syncope (e.g., lightheadedness, feeling of warmth, sweating, nausea, vomiting)
- After sudden unexpected unpleasant sight, sound, smell, or pain
- After prolonged standing or crowded, hot places
- During a meal or postprandial
- Triggered by cough, defecation, or micturition
- With head rotation or pressure on carotid sinus (e.g., tumor, shaving, tight collars)
- Standing from supine/sitting position

High risk (red flag):

Major

- New onset of chest discomfort, breathlessness, abdominal pain, or headache
- Syncope during the exertion (not after it has stopped), or when supine
- Sudden onset palpitation immediately followed by syncope

Minor (high risk only if associated with structural heart disease or abnormal electrocardiogram; ECG):

- No warning symptoms or short (<10 s) prodrome
- Family history of sudden cardiac death (SCD) at young age
- Syncope in the sitting position

Past Medical History

Low risk:

- Long history (years) of recurrent syncope with low-risk features with the same characteristics of the current episode
- Absence of structural heart disease

High risk (red flag):

Major

- Severe structural or coronary artery disease (heart failure, low left ventricular ejection fraction; LVEF or previous myocardial infarction)
- Family history of sudden/early/unexplained death (may be the only indication of an inherited channelopathy). While some have ECG evidence (e.g., long/short

QT syndrome, Wolff–Parkinson–White Syndrome (WPW), Brugada syndrome) others have none (e.g., catecholaminergic polymorphic ventricular tachycardia; CPVT)

Physical Examination

Low risk:

- Normal examination

High risk (red flag):

- Unexplained systolic blood pressure (BP) in the ED <90 mmHg
- Suggestion of gastrointestinal bleed on rectal examination
- Persistent bradycardia (<40 beats/min; bpm) in awake state and in absence of physical training
- Undiagnosed systolic murmur

ECG

Low risk:

- Normal ECG (Physician should seek advice if unsure).

High risk (red flag):

Major

- ECG changes consistent with acute ischemia
- Mobitz II second- and third-degree atrio-ventricular (AV) block
- Slow atrial fibrillation (AF) (<40 bpm)
- Persistent sinus bradycardia (<40 bpm), or repetitive sinoatrial block or sinus pauses >3 s in awake state and in absence of physical training
- Bundle branch block, intraventricular conduction disturbance, ventricular hypertrophy, or Q waves consistent with ischemic heart disease or cardiomyopathy
- Sustained and non-sustained ventricular tachycardia (VT)
- Dysfunction of an implantable cardiac device (e.g., inappropriate shock from implantable cardioverter defibrillator; ICD, or dysfunctional pacemaker)
- ST-segment elevation with type 1 morphology in leads V1–V3 (Brugada pattern)
- QTc >460 ms in repeated 12-lead ECGs indicating long QT syndrome (LQTS)

Minor (high risk only if history consistent with arrhythmic syncope)

- Mobitz I second-degree AV block and 1° AV block with markedly prolonged PR interval
- Asymptomatic inappropriate mild sinus bradycardia (40–50 bpm), or slow AF (40–50 bpm)
- Paroxysmal supraventricular tachycardia (SVT) or atrial fibrillation with rapid ventricular rates (especially in the elderly)
- Pre-excited QRS complex
- Short QTc interval (≤ 340 ms)

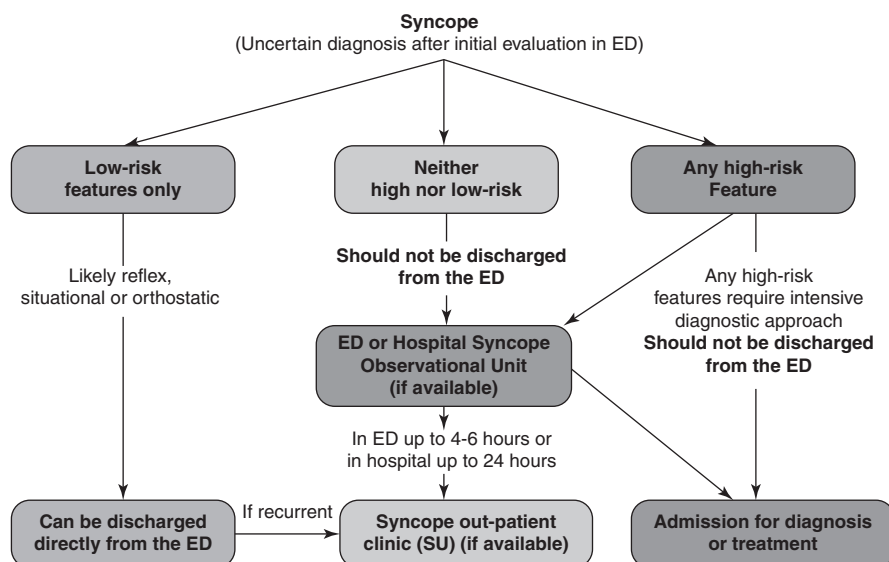


Fig. 12.1 Emergency department risk stratification flowchart to determine syncope patient management. *SU* syncope unit. Reproduced from Brignole et al. [1]. Reprinted by permission of Oxford University Press on behalf of the European Society of Cardiology

- Atypical Brugada patterns
- Negative T waves in right precordial leads, epsilon waves suggestive of arrhythmogenic right ventricular cardiomyopathy (ARVC)

Patients with prodrome, recurrent syncope, no structural heart disease, normal ECG, normal physical examination, and no injury are at low risk of serious short-term outcome. Patients with no associated prodrome or typical precipitating event, syncope when supine or during exertion, family history of sudden cardiac death at a young age, a past medical history including structural heart disease or an abnormal physical examination or ECG are at greater risk of cardiac syncope. Once ED risk stratification has been undertaken, the ESC ED risk stratification flowchart shown in Fig. 12.1 should be used to determine subsequent management [1].

12.4 Clinical Decision Rules

There are many ED Clinical Decision Rules (CDRs) and risk stratification tools for syncope that use medical history, examination, and ECG findings to stratify patients by their risk of developing both short- (i.e., 7–30 day) and long-term (i.e., 1 year) serious outcomes. Examples of these include:

- ROSE rule [4]
- San Francisco syncope rule [5, 6]

- OESIL [7]
- STePS [8]
- Canadian syncope risk score [9]

It is worth noting that none of these outperform clinical judgment [10], all tend to have low specificity thus increasing hospital admissions, and have been variably adopted. Some rules and tools have included age as a factor. While older patients are undoubtedly at higher risk of an adverse outcome after syncope, including age in such tools only reduces their specificity—leading to over admission.

12.5 Biomarkers

Although there is increasing interest in the use of biomarkers such as troponins and brain natriuretic peptides for ED syncope risk stratification, these cannot be recommended for routine care at present [11–15].

12.6 Red Flag Features not to Be Missed

Patients with the following are at risk of cardiac syncope:

- No associated prodrome or typical precipitating event
- Syncope when supine or during exertion
- Family history of sudden cardiac death at a young age
- Past medical history including structural heart disease
- An abnormal physical examination or ECG

Exercise-associated syncope is defined as syncope occurring during exercise. Although most cases are benign (especially those associated with post-exercise collapse which are commonly reflex) patients with exercise-associated syncope include groups of patients at high risk of sudden death and conditions such as arrhythmogenic right ventricular cardiomyopathy (ARVC), Brugada syndrome, and hypertrophic cardiomyopathy (HCM). Patients with trauma (commonly facial due to loss of consciousness, meaning they are unable to put their hand out) and those without prodromes and/or without apparent triggers and/or atypical presentation (termed non-classical reflex syncope forms) should be considered for further arrhythmia investigation even if they are of younger age. This is because arrhythmic syncope is associated with no or less than 3 s of prodrome, while the prodrome lasts up to 3 min in reflex syncope.

12.7 Does My Patient Need to Be Admitted to Hospital?

About half of all patients who present to hospital with syncope/collapse will end up being admitted. This is likely to be due to a lack of supporting outpatient services (e.g., syncope clinical decision/ED ambulatory unit or rapid access syncope clinic) and the concern of the clinician that the patient might be at risk of arrhythmic syncope. In fact, death within 7–30 days of ED attendance with syncope is infrequent at approximately 0.8% [1]. Non-fatal serious outcome (e.g., acute myocardial infarction, life-threatening arrhythmia, decision to implant a pacemaker or cardiac defibrillator, pulmonary embolus, cerebrovascular accident, intracranial hemorrhage, subarachnoid hemorrhage, hemorrhage requiring a blood transfusion, etc.) within 7–30 days of ED attendance with syncope is about 10.5% although in two-thirds of these patients the serious outcome was apparent in the ED. This suggests that many patients who are currently admitted could safely undergo a short period of ED monitoring plus selected echocardiography (if structural/valvular heart disease or heart failure is suspected) in an ED clinical decision/ambulatory unit, followed by urgent review by a syncope specialist in a rapid access syncope clinic. If this setup is not available, then patients at risk of cardiac syncope should not be discharged from hospital until advanced investigations such as echocardiography, ECG monitoring and review from an expert in syncope have been completed.

12.8 How Should I ECG Monitor My Patient?

In addition to the 12-lead ECG, immediate ECG monitoring should be applied when there is a suspicion of arrhythmic syncope. The new ESC guidelines [1] support an increased role for prolonged ECG monitoring when arrhythmic syncope is suspected. Establishing a cardiac arrhythmia as the cause of syncope rests on correlating the arrhythmia with symptoms using monitoring devices, but these all have significant drawbacks. Cardiac arrhythmia investigation is usually initiated with the Holter monitor, but non-compliance and lack of extended monitoring reduce diagnostic yield to less than 20%. Event recorders can monitor over longer periods of time but must be activated and cannot detect asymptomatic arrhythmias. External continuous loop recorders are expensive, require electrodes and bulky recording devices, and produce a large amount of data, which requires sifting. Implantable loop recorders are expensive and necessitate an invasive surgical procedure albeit minimal.

There is also very little evidence to support how long patients suspected of having arrhythmic syncope should be monitored for, either in the hospital or outpatient setting. The optimum duration of hospital ECG monitoring after the index episode is unclear but is likely to lie between 4 and 24 h. Hospital ECG monitoring should

occur in an area in which resuscitation facilities are available. Various times for outpatient ECG monitoring have been suggested, from 24 h to 28 days. The PATCH-ED study, which used an ambulatory ECG monitor in ED patients with unexplained syncope, identified a symptomatic significant arrhythmia in 1 in 10 patients and a diagnostic finding in 3 in 4 [16]. In this study, a third of the significant and symptomatic significant arrhythmias were captured within the first 24 h (suggesting a role for prolonged monitoring in the ED or in hospital). The majority of the significant and symptomatic significant arrhythmias were captured in the first 7 days, but some significant arrhythmias (mainly non-serious and asymptomatic) were picked up between days 8 and 14.

12.9 Driving

There have been a number of high-profile cases of syncope while driving leading to serious consequences [17]. It is vital that all people presenting with syncope are assessed for and counseled with respect to their fitness to drive, and that this is detailed in their medical notes. Current local fitness to drive guidelines might not always be easily recalled but should be available to access in the ED. Note that while guidelines will be very different in every country (and often within different regions of the same country as in the USA), in the UK, any patient with suspected cardiovascular syncope, cough syncope, or unexplained syncope and any Class 2 (Heavy Goods Vehicle) driver with vasovagal syncope must not drive from the time of their index presentation (Fig. 12.2). Patients who have been told to refrain from driving should be referred to a syncope specialist to confirm the diagnosis and receive ongoing driving advice. Please refer Chap. 27 for more details.

12.10 Should My Hospital Have a Syncope Clinical Decision Unit?

The current use of observation wards and syncope clinical decision units is not widespread; for example, only 27% of UK EDs have an observation ward that admits syncope patients [18]. The new ESC syncope guidelines promote the use of syncope clinical decision units within the ED. They allow a period of ECG monitoring for patients thought to be at risk of arrhythmic syncope and selected echocardiography if structural or valvular heart disease, or heart failure, is suspected. Shen et al. [19] showed that a designated syncope unit in the ED, where patients could stay for up to 6 h, significantly improved diagnostic yield in the ED and reduced hospital admission and total length of hospital stay, without affecting recurrent syncope and all-cause mortality. Patients underwent continuous cardiac monitoring, hourly vital sign check, echocardiography in patients with abnormal cardiovascular examination findings or an abnormal ECG, tilt-table testing, and electrophysiological

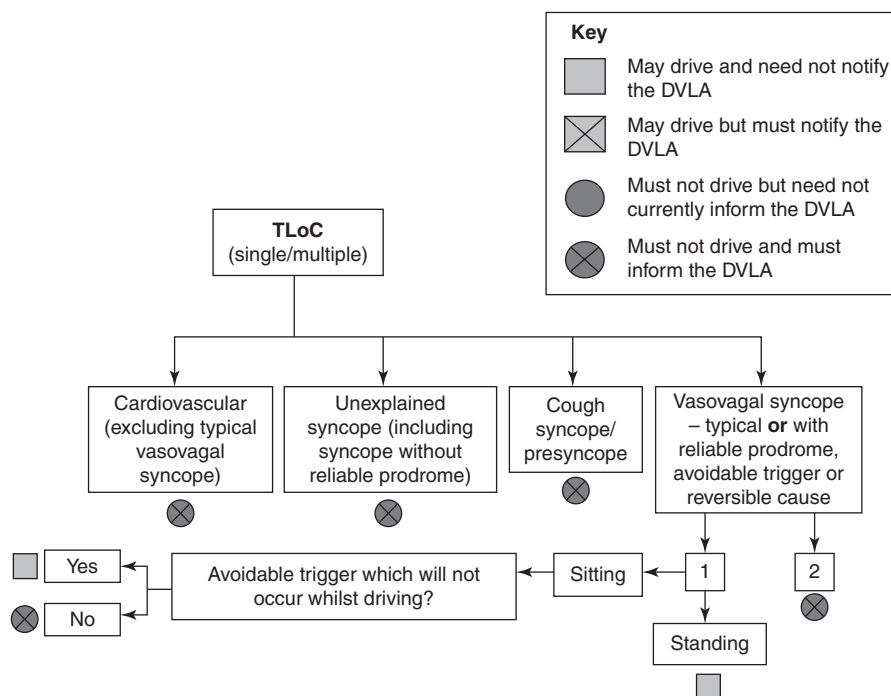


Fig. 12.2 UK fitness to drive in TLoC (adapted from A. Hudson, S. Saunder, R. Grant, St. George's University Hospital, London and based on March 2018 UK Driving and Vehicle Licensing Authority; DVLA advice. 1 = UK Class 1 driver's licence, 2 = UK Class 2 Heavy Goods Vehicle driver's licence)

consultation if indicated. Similarly, Sun et al. [20] showed that an ED observation syncope protocol reduced admissions, length of hospital stay, and index hospital costs, with no difference in safety events, quality of life, or patient satisfaction. Patients in this study received continuous cardiac monitoring, echocardiogram (for patients with a cardiac murmur on chest auscultation), and additional testing at the ED clinician's discretion. Guidelines on setting up a syncope clinical decision unit are also available through the ESC [21].

12.11 Should My Hospital Have a Rapid Access Syncope Clinic?

The current use of specialist syncope outpatient clinic is also not widespread; for example, only 18% of UK EDs have access to a specialist syncope outpatient clinic [18]. The new ESC syncope guidelines promote the use of rapid access syncope clinics as a safe way to reduce admissions and ensure patients receive timely, focused expert opinion and investigation. Setting up a syncope rapid access syncope clinic in

your hospital requires a multidisciplinary team approach, including emergency medicine, acute medicine, care of the elderly, neurology, cardiology, electrophysiology, nursing, cardiac imaging and neurophysiology, keen enthusiasts (a syncope site champion), and a lot of energy. All these disciplines do not need to be co-located, and in the simplest form can be brought together in a virtual clinic joined through a well-constructed pathway that signposts referring ED, acute medical and GP clinicians to the right place for their patient—be that the TIA/ stroke clinic, neurology clinic, first seizure clinic, general cardiology clinic, electrophysiology clinic, admission or the rapid access syncope clinic. There are no recommendations as to the timing of when patients requiring syncope clinic follow-up should be seen but sooner the better. If the patient was not seen by a syncope specialist in the ED observation facility or while an inpatient this should be on an urgent basis within 2 weeks.

12.12 Conclusion

Patients with syncope/collapse commonly present to the ED and present a major workup and disposition challenge. The 2018 European Society of Cardiology (ESC) syncope guidelines suggest an approach initially making a diagnosis of syncope (versus non-syncope ‘collapse’) and seeking an underlying cause. If no obvious underlying cause is found, risk stratification should determine risk of adverse outcome. Red flag symptoms should be considered and implications for driving should be fully considered. Establishing a hospital syncope clinical decision unit and rapid access syncope clinic is likely to reduce admissions, reduce length of hospital stay, and reduce hospital costs.

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Chapter 13

TLOC/Collapse: The Role of the Emergency Department Observation Unit



Ivo Casagrande

Abbreviations

ED	Emergency department
OU	Observation unit
SOU	Syncope observation unit
SU	Syncope unit
EDOU	Emergency department observation unit

13.1 Introduction

The Emergency Department (ED) Observation Unit (EDOU) is an area, generally located near the ED, that is dedicated principally to patients affected by potentially life-threatening clinical conditions, in whom: (1) a diagnosis has not been achieved during the ED evaluation, or (2) an acute unresolved condition is likely to be resolved with a further short (some hours) intensive observation. One-third of US hospitals currently have EDOU [1]. In Europe, Italy is probably the country with the largest number of EDOU's, about 400; EDOUs are present inside both level I and II EDs and are mostly directed by emergency physicians; they are called Short Intensive Observation Unit in order to emphasize the intensity of clinical and if needed invasive observation and treatment.

According to the Centers for Medicare and Medicaid Services (CMS) definition: "Observation care is a well-defined set of specific, clinically appropriate services, which include ongoing short-term treatment, assessment, and reassessment before a decision can be made regarding whether patients will require further treatment as hospital inpatients or if they are able to be discharged from the hospital usually with

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arrangements for outpatient follow-up care. Observation services are commonly ordered for patients who present to the emergency department and who then require a significant period of treatment or monitoring in order to make a decision concerning their ultimate hospital admission or discharge [2].

Emergency medicine physicians run most OUs. The observation time in some countries varies from 24 to 48 h. The most frequently admitted patients are those with a single problem to solve such as chest pain, headache, abdominal pain, or transient loss of consciousness (T-LOC, including syncope). In a large cohort of patients recently studied by the author, the two main complaints admitted to EDOU were syncope/collapse and chest pain, which accounted for 22% and 23%, respectively, of total EDOU admissions. As an example, a patient with chest pain can be discharged within 24 h if the ECG monitoring, serial troponin measurements and, sometimes, a non-invasive cardiac stress testing are negative. A patient with an unresolved acute asthma attack, after the initial treatment in the ED, can stay in EDOU for further 24–48 h and then, be discharged or admitted as appropriate. EDOU's are staffed with physicians and nurses, generally rotating with the pool of ED personnel and are equipped with multiparametric monitors and other instruments similar to those used for admitted patients. The management is based on pre-established standardized protocols.

13.2 Syncope Observation Unit and Its Role in Managing Syncope

Approximately 1–2% of all ED visits occur due to a chief complaint of syncope/collapse and these ED visits later account for 3–6% of hospital admissions. The clinical assessment of these patients is challenging because most are asymptomatic upon arrival and the differential diagnosis is broad, ranging from benign etiologies to life-threatening cardiovascular conditions; often, the underlying cause of a syncope episode cannot be clearly identified in the ED.

Being able to rule out life-threatening causes is one of the main goals of the emergency physician. Although diffusion of guidelines into clinical practice has substantially improved the management of patients with syncope/collapse in recent decades, hospital admission rates remain high, compared to the relatively low incidence of short-term events; in addition, about half of the admitted patients will be discharged with no clear diagnosis. Consequently, there is need for an observation period—longer than that can be possible in ED—in order to prevent unsafe discharges and, on the other hand, there is the need to avoid unnecessary hospital admissions.

ED-based observation protocols are an alternative approach to ordinary admissions and unsafe discharges. Several experiences reported in literature support this latter notion. An early study, published by Shen et al. [3], was the Syncope Evaluation in the Emergency Department Study (SEEDS). The primary aim and central hypothesis of the study was whether an area designated for syncope/collapse evaluation in

the ED could affect diagnostic yield and reduce the rate of hospital admissions for syncope patients with intermediate-risk. The study included patients who presented with collapse of undetermined cause who had an intermediate risk for an adverse cardiovascular outcome. It was a prospective, randomized, single-center study. Patients were randomly allocated to two treatment arms: evaluation in EDOU or standard care. All patients met the criteria for hospital admission. Patients randomly assigned to syncope observation unit (SOU) received continuous cardiac monitoring for up to 6 h. The model based on SOU significantly improved the rate of etiological diagnoses (10% in standard care versus 67% in SOU group). It was effective in lowering both hospital admission rate (43% in SOU vs. 98% in the standard care group) and the total length of hospital stay in the cases of hospitalization (total patient-hospital days reduced from 140 in standard care to 64 in the SOU group). In another study, Rodríguez-Entem et al. [4] applied the diagnostic algorithms of ESC guidelines on syncope strictly and continuously monitored patients in a dedicated area of the ED. They reached a 78% rate of diagnoses, with only a 10% rate of hospital admissions. Their syncope protocol, based on the early detection of heart disease, was based on a multidisciplinary collaboration between medical personnel of both emergency department and arrhythmia unit. The availability of a number of dedicated beds in the SOU, where the patient was monitored up to 24 h until they were discharged or admitted, made the application of this protocol possible. In another report, Sun et al. [5] hypothesized that an ED observation syncope guidelines-based protocol might safely reduce hospitalizations in patients aged over 50, at intermediate risk. They compared the ED observation syncope protocol versus routine inpatient admission. All study patients received an initial ED evaluation consisting of a directed history, physical examination, standardized laboratory tests, and a 12-lead ECG; moreover, all patients assigned to the observation protocol received continuous ECG monitoring for at least 12 h; the maximum stay in the EDOU could not exceed 24 h. The results showed that there was a lower hospital admission rate (15% vs. 92%), shorter mean hospital length of stay (29 vs. 47 h), and lower hospital costs (mean cost at index visit 1400 vs. 2420 US dollars) in patients assigned to the observation protocol compared to controls. There were no differences in the rate of short-term serious outcomes after hospital discharge, general health utility, syncope-specific quality of life, and patient satisfaction in the two groups. More recently, Ungar et al. [6] investigated whether the availability of a SOU combined with an in-hospital SU could reduce the hospitalization admission rate and major clinical outcomes. Neither specific protocols nor risk stratification was applied. The study showed that the combination in the same hospital of both an SOU and a SU significantly improved diagnostic performance, without increasing short-term adverse events.

In a retrospective study, Grossman et al. [7] assessed the differences in outcomes and diagnoses between 1-day inpatient full hospitalization and SOU stays for syncope. The syncope patients were divided in three cohorts: 1-day admission to an inpatient ward, admission to SOU, or full hospitalization. Risk stratification was not used. The determined etiology of syncope did not differ substantially among the groups, being 74% of patients fully admitted, 64% of patients with a 1-day

admission, and 64% of those evaluated in the SOU. Numeroso et al. [8] performed a meta-analysis of the six above studies. They concluded that the SOU proved the best management owing to the elevated diagnostic yield and low incidence of short-term adverse events.

13.3 Management of Syncope in the Emergency Department Syncope Observation Unit, According to Risk Stratification

When syncope/collapse remains of undetermined origin after the initial evaluation in ED, patients at high- and intermediate-risk should be identified and evaluated in the SOU [9–11]. In particular, the ESC 2018 guidelines [11] give precise guidance (Fig. 13.1) which are based on the literature and “experts” opinions (Table 13.1). Interestingly, use of formal risk stratification scores obtained a low strength of recommendation (IIb), since many argue that experienced physician judgement is as effective. In any case, the ESC 2018 guidelines have expanded the most common

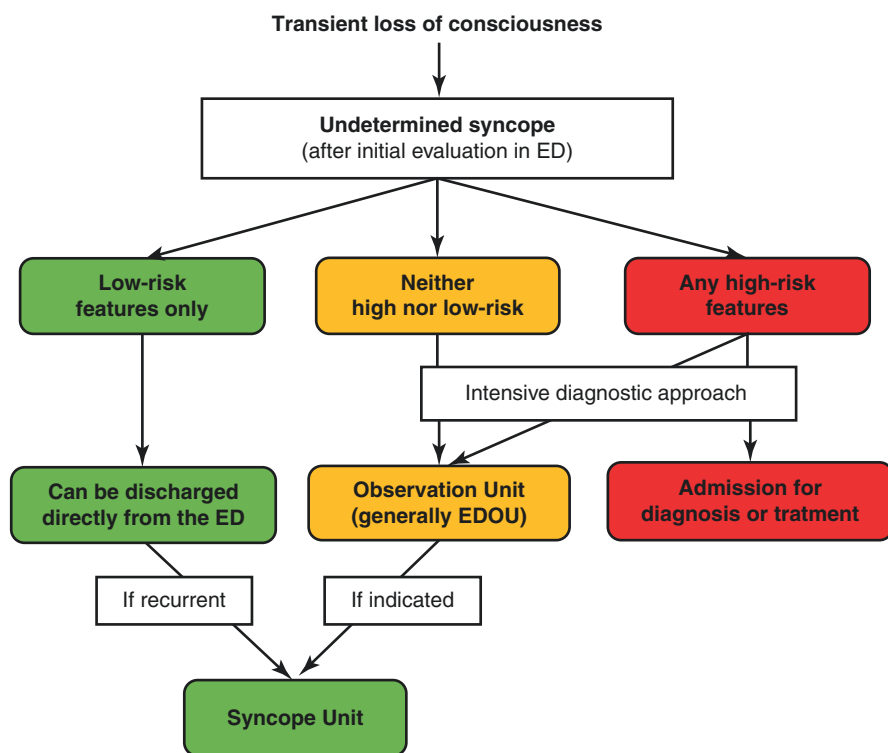


Fig. 13.1 Emergency Department: undetermined syncope management according to risk stratification. Adapted from Brignole et al. [11]

Table 13.1 Management of syncope in the ED

Recommendations	Class ^a	Level ^b
It is recommended that patients with low-risk features, likely to have reflex or situational syncope, or syncope due to OH, are discharged from the ED	I	B
It is recommended that patients with high-risk features receive an early intensive and prompt evaluation in a syncope unit or in an ED observation unit	I	B
It is recommended that patients who have neither high- nor low-risk features are observed in the EDOU or in a SU	I	B
Risk stratification score perform no better than good clinical judgement and should not be used alone to perform risk stratification in the ED	IIb	B

Adapted from Brignole et al. [11]

OH orthostatic hypotension

^aClass of recommendation

^bLevel of evidence

Table 13.2 Criteria favoring a stay in an emergency in an EDOU

Stable, known structural heart disease
Severe chronic disease
Syncope during exertion
Syncope while supine or sitting
Syncope without prodrome
Palpitations at the time of syncope
Inadequate sinus bradycardia or sinoatrial block
Suspected device malfunction or inappropriate intervention
Pre-excited QRS complex
SVT or paroxysmal atrial fibrillation
ECG suggesting an inheritable arrhythmogenic disorder
ECG suggesting ARVC

Adapted from Brignole et al. [11]

ARVC arrhythmogenic right ventricular cardiomyopathy, SVT supraventricular tachycardia

conditions that favor a stay in SOU; of note, many of these criteria are usually considered high-risk criteria (Table 13.2).

During SOU stay the patient should undergo a careful process that includes two mandatory steps for all patients, i.e., clinical reassessment and cardiac rhythm monitoring, and three optional steps, depending on the result of clinical evaluation and the patient features, i.e., radiologic and laboratory tests, syncope-specific exams, and syncope expert or specialist’s consultation.

13.3.1 Mandatory Steps

1. *Reassessment.* Due to the difficulties related to the limited time available in ED, patients, particularly those with high-risk features, should receive a prompt and intensive reassessment in order to retrieve further diagnostic elements from the history and physical examination and provide a more precise risk stratification.

2. *Monitoring.* The monitoring should be clinical and technologic (multiparametric monitoring such as ECG, blood pressure, and oxygen saturation). The rationale of the monitoring is that if the patients not at low risk would have an arrhythmic syncope, the probability to detect an arrhythmia is higher the hours immediately after the syncopal event (1.9–17.6%) [11]; another reason is the need to avoid a possible immediate risk to the patient. According to a study from Solbiati et al. [12], monitoring should be continued for at least 12–24 h. Thiruganasambandamoorthy et al. [13] conducted a prospective cohort study on patients presenting in ED within 24 h of the syncopal event who were stratified according to the Canadian Syncope Risk Score. All patients received ECG monitoring for 30 days. One-half of arrhythmic outcomes were identified within 2 h after ED arrival in low-risk patients and within 6 h in medium- and high-risk patients. Overall, 91.7% of arrhythmic outcomes among medium- and high-risk patients, including all ventricular arrhythmias, were identified within 15 days

13.3.2 *Optional Steps*

1. *Tests and exams.* Radiologic and laboratory tests have a low diagnostic yield. Only occasionally are they be useful to confirm the results of laboratory tests already requested in ED. Brain CT should be requested only in those with head trauma during syncopal event. However, apart from evaluating trauma, brain imaging has little utility in most syncope/collapse patients. Carotid sinus massage should be performed in supine and standing position in patients aged >50 years when there is a suspicion of reflex syncope. An echocardiogram is warranted when there is a suspicion of structural heart disease or for syncope secondary to cardiovascular cause, and stress testing may be reasonable for patients who have experienced episodes of syncope during or shortly after exertion.
2. *Specialist consultation.* Neurological consultation is useful if an epileptic disorder or a psychogenic form of collapse is suspected. Geriatric consultation is warranted in case of unexplained falls in elderly people with comorbidities or frailty.
3. *Syncope expert consultation.* According to the EHRA position statement on the Syncope Unit, the syncope specialist is a physician who has sufficient knowledge of historical clues and physical findings to recognize major T-LOC forms, including mimics, as well as syndromes of orthostatic intolerance [14]. A discussion between the syncope specialist and the ED physician can be useful to improve the diagnostic yield, as well as to organize a fast track of the patients to the in-hospital SU.

13.4 **SOU Organization**

The SOU should be an integral part of the OU inside the ED, with which it shares the medical and nursing staff. The SOU should be equipped with multiparametric monitors for ECG and non-invasive BP monitoring (NIBP). It must also be equipped

Table 13.3 SOU organization

Tests and consultancy	Details
ECG and BP monitoring	ECG and NIBP collection and 24 h or longer storing
Active standing test	Standing test with intermittent NIBP
Carotid sinus massage	Supine and standing carotid sinus massage under ECG and NIBP monitoring, according to the method of symptoms in patients older than 50 years, when indicated
Echocardiogram	Echocardiogram, when indicated by suspected presence of structural cardiac disease
Blood tests	Blood tests, when indicated by suspected conditions such as anemia, electrolyte/glucose abnormality, thyroid disorder, etc.
Syncope expert	Syncope expert consult, shared management protocol and fast track referral to SU
Expert consults	Cardiologist, Geriatrician, Neurologist, Psychiatrist

Adapted from Brignole et al. [11]

ECG electrocardiogram, *BP* blood pressure, *NIBP* non-invasive blood pressure

for ACLS interventions. According to the Italian Multidisciplinary Group for Syncope Study (GIMSI) experience, SOU should have a protocol for the management of the T-LOC patients, shared with the SU and other specialists who can also offer consultation (cardiologists, neurologists, psychiatrists and geriatricians) [15]. For more specific tests (e.g., tilting test, standing carotid sinus massage) and for the access to syncope expert consultancy, patients should be referred to the in-hospital SU, according to the local syncope protocol (Table 13.3). The length of stay should be no less than 6 h and no greater than 36.

13.5 Syncope Observation Unit and Syncope Unit

A SU is defined as a facility featuring a standardized approach for the diagnosis and management of in-hospital and outside patients with transient loss of consciousness and related symptoms. The SU organization, with dedicated staff and access to appropriate diagnostics and therapies, is described in the Chapter 16. According to published experiences [3–5], in those hospitals that have a SU, SOU and SU share common protocols and pathways. Thus, SOU acts as the functional part of the SU where ED syncope patients should be referred when it is necessary to proceed with 2° step investigations and treatment.

13.6 Conclusion

A syncope observation unit (SOU), as part of an OU in the ED, represents a good solution in managing the intermediate and high-risk patients with undetermined syncope/collapse after ED evaluation. The SOU should be well equipped, and the

ED physician running this unit should have at least a basic competence in syncope management. It is also essential that there is a shared syncope protocol with the local SU syncope expert and with other specialists that can serve as consultants in management of syncope/collapse patients.

Conflict of Interest No one.

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Chapter 14

Ambulatory ECG Monitoring in Syncope and Collapse: Current Status and Utility



Richard Sutton and David G. Benditt

14.1 Introduction

Syncope and collapse (syncope/collapse) are among the most frequent diagnoses attending Emergency Departments (ED) in the United States (US) and Europe [1, 2]. While outcomes are mostly benign, syncope/collapse may nonetheless cause injury, adversely impact quality-of-life, and point to increased mortality risk [3, 4]. Consequently, prevention of future syncope/collapse is important, demanding the attention of clinical cardiac electrophysiologists as well as the wide range of other practitioners who encounter these patients.

Practice guidelines from professional societies offer strategies for determining the etiology of syncope/collapse [5–7]. In brief, if a cause is not apparent after initial careful medical history and physical examination plus a few selected laboratory tests, as indicated (e.g., ECG, echocardiogram), the next steps recommended are appropriate use of short- or longer-term diagnostic ambulatory ECG (AECG) [5–7]. The desired goal is to capture an ECG recording during a spontaneous symptom episode; such a recording may document a causal arrhythmia, or alternatively eliminate arrhythmia as the basis for symptoms. Less desirable, but nonetheless a potentially useful finding, is that of a sufficiently worrisome asymptomatic arrhythmia (e.g., very rapid but unsustained ventricular tachycardia), that if it were sustained, might be expected to result in the patient's syncope/collapse.

In regard to selection of diagnostic AECG monitoring devices, guidelines recommend use of Holter monitors when events are very frequent (e.g., daily or almost

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daily), wearable event monitors or mobile cardiac telemetry (MCOT) for less frequent episodes (e.g., weekly to monthly), and insertable cardiac monitors (ICMs) for less frequent symptoms. However, several studies undertaken after the publication of relevant guidelines suggest that while most physicians follow the published recommendations in most circumstances, a substantial minority of others do not [8, 9]. Further, in regard to syncope/collapse patients in whom diagnostic AECG monitoring is prescribed, there is little known regarding their understanding of the array of AECG devices available and the factors that drive choices among them [10]. Greater patient understanding would be expected to improve compliance and enhance diagnostic utility of AECGs, especially in regard to documenting arrhythmia-symptom correlations.

14.2 Physician Practice Findings

Several surveys, performed in 2015–2016 [8, 9] examined “real world” physician use of diagnostic AECG monitoring technology in evaluation of syncope/collapse. The sponsor for all studies was Medtronic Inc. but sponsor personnel did not participate in recording or interpreting the observations.

Requests to participate in the surveys were sent to a geographically diverse sample of physicians comprising various specialties. Respondents were asked to exclude patients with accidental falls or known epileptic seizures from their responses.

The US physicians surveyed encompassed all major geographical regions of US. Practice locations were 85% urban and 15% rural. Years in clinical practice ranged from 12 to 20 years. Figure 14.1 illustrates that while cardiologists use AECG monitoring the most, AECGs are nonetheless widely used by physicians of a wide range of specialties.

In the US study, responding physicians comprised 6 specialties:

1. ED physicians ($n = 35$),
2. primary care practitioners ($n = 35$),
3. hospitalists/internists ($n = 30$),
4. neurologists ($n = 30$),
5. cardiologists who were not device implanters (non-implanting cardiologists, $n = 34$), and
6. cardiologists who implant devices (implanting cardiologists $n = 35$).

The European physician cohort comprised 33 ED physicians from UK and 40 from Germany; cardiologists were 54 from UK and 50 from Germany. Among the cardiologists, there were 14 UK and 20 German physicians who were not device implanters (non-implanting cardiologists, $n = 34$), the remaining 40 UK and 30 German cardiologists were device implanters (Implanting UK and German cardiologists $n = 70$). MCOT devices were not available in Europe at the time of these studies.

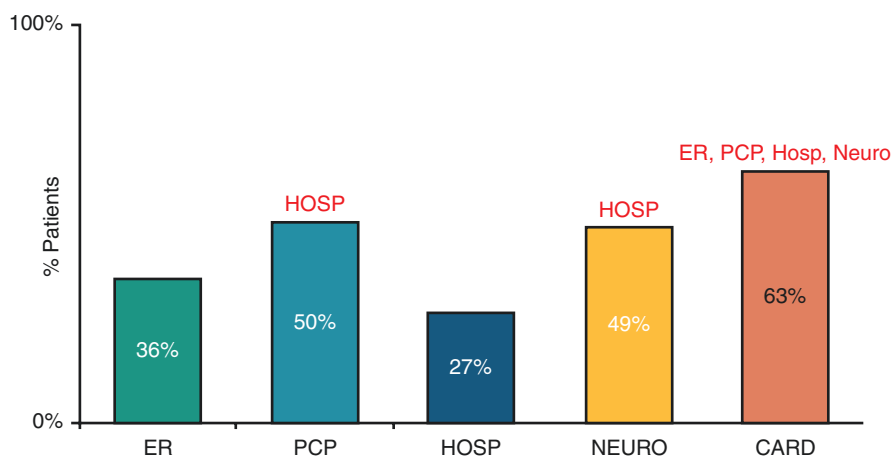


Fig. 14.1 Percentage of physicians by specialty who report using AECG techniques to evaluate patients presenting with syncope/collapse. Above each patient specialty bar, the Red lettering indicates a statistical significant difference $p < 0.05$. *ER* Emergency Department, *PCP* primary care providers, *HOSP* hospitalists, *NEURO* neurologists, *CARD* cardiologists

14.2.1 US Physician Observations

Physician respondents in the US study were asked to estimate the proportion of syncope/collapse patients in whom they use AECG monitoring as part of the diagnostic evaluation. Findings varied by specialty, ranging from 25 to 30% for primary care physicians, to in excess of 60% for cardiologists. The primary factors that triggered physicians to proceed with AECG diagnostic monitoring were: (1) findings suggesting underlying cardiac disease or channelopathy, (2) a report of palpitations, or (3) physical injury with collapse.

In addition, among syncope/collapse patients in whom structural cardiac disease was not suspected, AECG monitoring was most often used if the following were found: (1) recurrent collapse and/or (2) no abnormalities having been identified despite completion of multiple other tests.

Respondents were asked to indicate their preferred AECG monitor technology given various expected syncope/collapse event frequencies. In the case of very frequent (i.e., daily) symptom events, 25% of respondents chose a technology other than a 24–48 h Holter. For events expected to occur once/week, physicians selected an Event recorder or MCOT (mobile cardiac outpatient telemetry) 74% of the time ($p < 0.05$ versus either Holter or ICM [insertable cardiac monitor]). Conversely for events expected to occur only once or less per year, an ICM was chosen 62% of the time ($p < 0.05$ versus Holter or Event recorder or MCOT). The latter usage rate seems low for infrequent events in which ICMs are generally the best choice, but use may be affected by patient-specific issues that are unrelated to device efficacy, such as: the invasive nature of the procedure, ICM availability in some regions, and insurance coverage limitations. In any case, these findings indicate that a substantial

minority of clinicians under “real world” conditions do not prescribe AECG systems as recommended by the guidelines.

The lower upfront cost of wearable devices versus ICMs was expected to be an issue, but was less commonly reported by physicians (20–50%) to be a limitation than was anticipated. Variation in familiarity with recent generation ICMs may also have contributed to low usage, with familiarity ranging from 37% of ED physicians to 100% among implanting cardiologists.

14.2.2 European Observations

Findings, from UK/Germany physicians comprised questionnaire responses from 177 physicians (73 ED and 104 cardiology). The years (yrs.) of practice experience for UK responders averaged 14.4 yrs. for ED physicians, 12.9 yrs. for non-implanting cardiologists, and 24.5 yrs. for implanting cardiologists. The respective values among German physicians were 12.9 yrs., 15.4 yrs., and 12.6 yrs., respectively. All UK ED physicians and 85% of German ED physicians worked in public hospitals. For non-implanting cardiologists, the UK and Germany public hospital percentages were 93% and 58%, respectively, whereas for implanting cardiologists the public hospital percentages were 98% and 82%, respectively.

Inasmuch as cardiologists were more likely than ED physicians to be aware of the ultimate syncope/collapse discharge diagnosis, the non-implanting and implanting cardiologists (NIC, IC) were questioned regarding the proportion of syncope/collapse diagnoses that they encountered as a percentage of all patients. There were no significant differences between UK and German cardiologists.

14.2.3 Factors Driving Monitor Technology Choice in Europe

Both ED physicians and cardiologists in the UK and Germany indicated that the most important driver of AECG technology choice was their impression of obtaining a useful diagnostic yield. Second in importance was the frequency with which TLOC recurrence was expected. In terms of device choice, both UK and German physicians tended to follow practice guidelines appropriate to their regions (NICE in UK [7] and ESC Guidelines in Germany [6]), but in each case there were important divergences, which were particularly notable among ED physicians who may reasonably be expected to be less familiar with cardiology practice guidelines than are Cardiologists.

Findings revealed that most UK ED physicians (80%) follow NICE guidelines [7] for use of a Holter for daily symptoms, but diverged from NICE recommendations for Holter recordings if the expected frequency of events was 2–3/week. In the latter circumstance, (73%) preferred event monitors or ICMs to Holters ($p < 0.05$). On the other hand, approximately 30% of these same physicians indicated, in

contradistinction to NICE recommendations for an ICM, that they would select a wearable event monitor or Holter recorder even for anticipated episode frequencies of less than every 6 months. The basis for this divergence from guideline recommendations warrants further exploration.

Among German ED physicians, 69% follow ESC guidelines [6] for choosing a Holter for daily symptoms ($p < 0.05$ vs Event and ICM); the remainder prefer longer-term monitors, but only 46–54% would follow ESC Guidelines for ICM use when event frequency is less than 6-monthly. About one-third of the surveyed UK ED physicians would continue with Holters or wearable event recorders. The comparable percentage for German physicians ranged from 15 to 25%.

The vast majority of UK Cardiologists (94%) follow NICE guidelines [7] recommendation of Holter for daily symptoms, but only 43% would follow NICE recommendation of Holter recordings for event frequencies of 2–3 times/week. Similarly most UK cardiologists (75–83%) follow NICE guidelines for ICM use when symptoms are expected less than 6-monthly.

German cardiologists also largely follow ESC guidelines [6] regarding use of Holter recorders for daily events (90%). In addition, 70% follow recommendations for Holter recorders when event rates are expected to be 2–3/week. Further, German cardiologists closely follow ESC guidelines for use of ambulatory monitors in patients with low frequency of symptomatic events. Thus, 76–82% would select ICMs in such conditions.

14.3 Follow-Up AECG Monitoring by US and European Physicians

Often, the initial diagnostic monitoring session may not provide a definitive actionable outcome. In such cases, physicians may decide to continue AECG monitoring for an additional period (i.e., “follow-up monitoring”). Physician preferences regarding the follow-up monitoring strategy were divided into ED physicians, cardiologists who practice primarily in hospitals, and cardiologists who are primarily office-based.

Findings revealed that many physicians persist with the same AECG methodology. Approximately 50% of US physicians across all specialties reported that although they have access to all AECG technologies, they tend to repeat the same wearable AECG technique despite failure to establish a diagnosis on a first attempt. This tendency ranged from as low as 33% for neurologists to as high as 62% for non-implanting cardiologists.

The principal explanations for repeating the wearable AECG monitoring rather than selecting ICMs were:

1. the non-invasive nature of wearable monitors (33–63%) despite the fact that ICM placement is minimal in terms of the nature of the procedure,
2. the ease of initiating external monitoring (43–55%) since certain devices may be “on the shelf” while ICMs may need procedure scheduling, and

3. the perceived burden of data transmitted from ICMs (20–53%). The latter is of particular concern in some of the more litigious geographies where overlooking a key tracing amidst a large volume of material could create legal problems.

Findings regarding follow-up monitoring were similar among European physicians as those in USA. In this regard, although differences were not statistically significant, the survey suggested that German physicians of both ED and cardiology specialties tended to repeat the same monitor methods more so than did UK physicians. The most important drivers were ease of use of an external monitor system (UK 73%, Germany 60%), and non-invasive nature of the monitor (UK 64%, Germany 60%).

14.4 Patient Understanding of AECG Use

Little is known regarding patient understanding of AECG technology and why one or other device was prescribed by their physician. In one study, findings were derived from individuals in the USA ($n = 99$), Germany/UK ($n = 75$), and Japan ($n = 40$) in whom AECG monitoring had been undertaken as part of the evaluation of syncope/collapse. As part of the survey, patients were questioned regarding their understanding of the attributes of the various available AECG technologies. Since not all patients had experienced all AECG methods, descriptive materials were supplied to cover all the modalities. Responses were graded using a Likert-like 7-point scale (0 = I don't know, 1 = Not important, 4 = Somewhat important, 7 = Very important with grades 5 and 6 offering the responder additional discrimination).

Concerning understanding of device function, USA patients provided the highest scores regarding appropriate use of Holter and event recorder systems. The USA scores did not however differ significantly from those in the EU, but were statistically higher than Holter or ICM scores of Japan patients. These findings are consistent with patient perception of the teaching that they received as part of the initiation of the diagnostic monitoring process. In essence, USA patients reported higher Likert scores for the education they received than did EU or Japan patients. The differences were statistically significant for Holters and ICMs. However, even the highest scores were such that patients indicated that greater educational effort is still needed.

Respondents were asked to rank the clinical attributes that they believed were most important in selection of diagnostic AECG technology for their symptoms (Fig. 14.2). The ability to detect a cause of syncope and to rule out a cardiac etiology were the most important issues identified across geographies. In this regard, USA patients were statistically more likely to indicate that the ability to detect a cause of syncope was crucial for use of Event recorders or ICMs than were patients in Japan

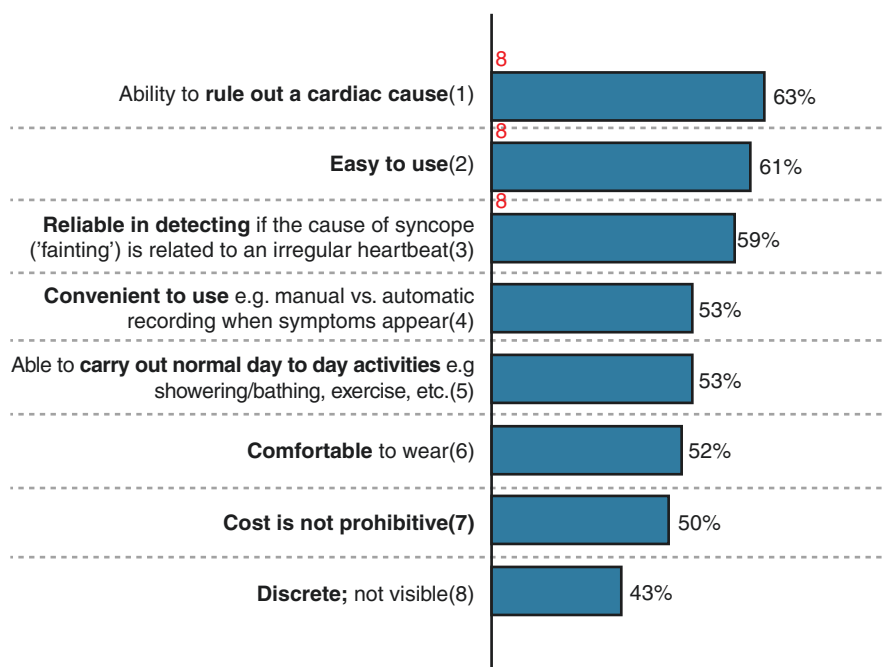


Fig. 14.2 Percent of USA patients ranking various AECG attributes as most important (i.e., Top 2 box on Likert scale). The Red numerals indicate that the attribute choice differed significantly from Attribute #8 (i.e., the Discrete nature of the device). See text for details

($p < 0.05$). The AECG being discrete (i.e., small and not apparent to others) ranked relatively low (Fig. 14.2). Further, while there were no statistically significant differences in patient perceptions regarding effectiveness of various AECG technologies for identifying or excluding a cardiac cause of syncope there was a trend for ICMs to rank higher among US patients compared with either EU or Japan patients.

The importance of cost as a determinant of the acceptability of an AECG technology was raised as a concern by only a minority of patients and the frequency of this concern was similar in the USA and EU patients and somewhat less in Japan. This difference among the technologies is not readily explained by other factors surveyed such as desire for more discrete recorders or greater ease of operation. Whether the nature of the patient's health insurance scheme plays a role merits further study, as cost is a lesser personal issue if payment is covered by national health insurance.

Apart from cost, an important minority of patients raised concerns regarding use of ICMs that merit being addressed as part of the discussion of an ICM recommendation in a given individual (Fig. 14.3). In particular procedural risk and scar size were issues that, while not frequently raised by most patients, were nonetheless topics that merit educational attention.

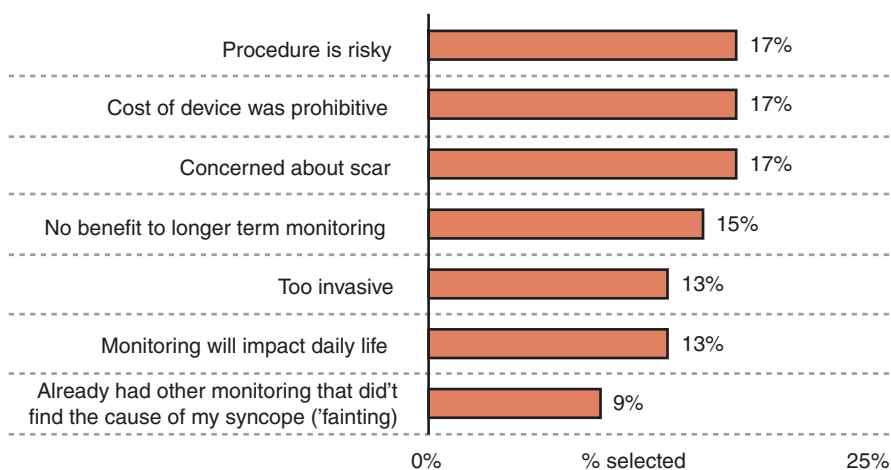


Fig. 14.3 USA patient concerns regarding physician recommendation that an ICM be placed for diagnosis of syncope collapse. Most patients accepted the recommendation but the concerns raised indicate items that merit being addressed during education of individual patients

14.5 Conclusion

Independent of specific discipline, physicians investigating syncope/collapse follow local AECG guidelines most of the time; however, an important minority do not. Thus, additional physician training regarding AECG applications is essential. Further, given the desire for optimizing patient compliance within AECG monitoring, especially in regard to documenting symptom-arrhythmia concordance (or lack thereof), findings indicate that patients both need and desire more detailed education regarding AECG device operation.

Conflicts of Interest RS declares that he is a consultant to Medtronic Inc., a previous grant holder for clinical studies from Medtronic Inc., serves on the speakers bureau of Abbott Laboratories Inc. and holds equity in Edwards Lifesciences Corp, AstraZeneca plc, and Boston Scientific Inc.

DGB declares that he is a consultant to and holds equity in Medtronic Inc, and Abbott Laboratories Inc, and has received support from the Dr. Earl E. Bakken family in support of Heart-Brain research.

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Chapter 15

Carotid Sinus Syndrome: Pathophysiology and Diagnosis



Jean-Jacques Blanc

15.1 Anatomy and Physiology

The carotid sinus, in human anatomy, is a dilated arterial area just superior to the bifurcation of the internal and external carotid arteries at the level of the superior border of thyroid cartilage. The carotid sinus extends from the bifurcation to the proximal part of the internal carotid artery. The sinus area is slightly dilated as the muscles of the tunica media are relatively thin at this level but, on the other hand, the tunica adventitia is thicker than usual. The baroreceptors, modified nerve endings attached to the cytoskeleton present within the nerve endings, are densely situated on the walls of the carotid sinus.

The baroreceptors, which are more appropriately termed “stretch receptors,” are pressure sensing bodies very sensitive to rapid changes in blood pressure (BP). When a rapid change in BP is detected by the baroreceptors, for example when a person changes from upright to supine position, the increase in BP causes stretch in blood vessels which results in movement of sodium ions into the nerves endings initiating an action potential. These baroreceptors have an intrinsic facility to generate action potentials at a particular frequency at baseline. When the baroreceptors receive a stretch stimulus secondary to increase in BP this frequency is increased. The upper limit for BP, after which the frequency of action potential stops increasing, is 175 mmHg. The normal mean arterial pressure is considered to be 93 mmHg and at this value, baroreceptors are believed to be the most sensitive and even slight changes in pressure will result in rapid firing of action potentials.

Afferent action potentials from the carotid sinus baroreceptors are transmitted by the Herring nerve, a branch of glossopharyngeal nerve, into the nucleus of tractus solitarius situated in the medulla. The vasoconstrictor center, the vasodilatory and the cardioinhibitory centers are also located within the medulla and lower third of

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the pons. These centers receive “structured” impulses from the nucleus of tractus solitarius which transmits efferent impulses via sympathetic and parasympathetic nerves to the heart and vessels. Impulses are carried to the heart mainly via the parasympathetic vagus nerve. Sympathetic impulses travel to the intermedio-lateral segment of the spinal cord which gives rise to efferent motor spinal nerves which enter the sympathetic ganglion running parallel to the spinal cord. Postganglionic sympathetic nerves ultimately reach the heart and the peripheral vasculature. Another pre-ganglionic sympathetic nerve also supplies the adrenal medulla which results in the release of epinephrine and norepinephrine, which contribute to a secondary enhancement of sympathetic activity. The final result is either an increase or decrease in BP, thereby correcting the initial disturbance in hemodynamics. To summarize, this baroreceptor reflex, like other reflex arcs, comprises three units:

- Afferent nerve carrying impulses from the carotid sinus baroreceptors
- Central processing unit situated in the upper medulla and pons
- Efferent parasympathetic and sympathetic nerves that innervate the effector organ (i.e., heart, blood vessels, etc.)

Massage of the carotid sinuses physically stretches the baroreceptors which mimics an increase in blood pressure. The rate of afferent impulse firing of the carotid baroreceptors is increased and the reflex arc responds by a shutdown of the sympathetic system and an activation of the parasympathetic system. This results in decrease of both BP and heart rate (HR).

15.2 Pathophysiology

The above-mentioned reflex eliciting slowing in HR and drop in BP during pressure on the carotid sinus has been recognized for a long time, perhaps even since the ancient Greek epoch. However, these induced modifications in HR and BP are only modest in the vast majority of the population. On the other hand in some individuals the response initiated by carotid sinus massage (CSM) is extremely amplified inducing a cardiac pause lasting several seconds and generally associated with a major fall in BP. By current clinical definition (albeit somewhat arbitrary and debated as noted later), when the ventricular pause lasts >3 s and/or the fall in systolic BP reaches >50 mmHg the finding is considered sufficiently abnormal to be termed carotid sinus hypersensitivity (CSH).

15.2.1 Epidemiology of CSH

Among 272 individuals older than 65 years sampled from a single general practice register, CSH was present in 107 (39%). Older age and male sex were the only predictors of CSH [1]. However, for some authors the diagnosis criteria summarized

above for CSH in older people are over sensitive and need to be revised (a pause in heart rate >7.3 s, and/or a drop >77 mmHg in systolic BP, or both is proposed). According to these new criteria the prevalence of CSH in the same population [1, 2] decreases to 10% [3]. In patients <40 years of age CSH is very exceptional and is particularly infrequent in females [4].

15.2.2 *Etiology*

Although baroreceptor function usually diminishes with age, the reason(s) why some older people, especially males, experience paradoxical hypersensitive carotid baroreflexes, even during mild stimulation of the neck, remains poorly understood. The site of the excessive sensitivity in the reflex arc remains speculative. The following summarizes some of the studies that have addressed the hypersensitivity issue.

For some researchers, due to the stiffness of the carotid sinus in most older people with CSH, the abnormal reflex has been attributed to disturbances at the baroreceptor level [5]; but if that were the case, how does one explain that some young healthy persons <40 years have CSH and many older people with carotid atheroma have not?

For others the defect is thought to be located at the level of the central nuclei. Afferent action potentials sent from the carotid sinus baroreceptors are considered appropriate but the processing in the central nuclei is abnormal and the efferent orders sent to heart and vessels through autonomic nervous system are totally overstated. This concept of diseased central nuclei is supported by the finding of increased tau protein accumulation in baroreflex associated nuclei in patients with CSH compared to those without [6]. But on the other hand, the functioning of central nuclei besides the nucleus of tractus solitarius was described to be absolutely normal in patients with CSH [7]. The latter is then an argument against the hypothesis of an organic central defect in the reflex pathway.

It is unlikely that the problem lies within the efferent part of the reflex arc as that would implicate multiple different sites of action (heart and many vessels). Furthermore, cardiac sympathetic neuronal activity has been described to be similar in patients with CSH and in control subjects [8].

In the mid-1990s an unexpected association between chronic denervation of the sternocleidomastoid muscle (but not other neck muscles) and CSH was reported [7, 9]. Although association does not mean causality, due to the close anatomical relationship between the two structures, it was tempting to elaborate a hypothesis that integrates this finding in the pathophysiology of CSH. It was suggested that the degenerative process of chronic denervation of the sternocleidomastoid muscles with aging interrupts normal integration of neck muscle proprioception and carotid baroreceptor information, leading to excessive responses to CSM [7]. This hypothesis was recently challenged by the observation that acute pharmacological block of the sternocleidomastoid muscles does not result in an increased response to CSM [10]. However, this latter study by Lloyd et al. [10] was performed in healthy young

individuals and with an acute pharmacological blockade of the muscle; this model is substantially different from a chronic, degenerative process in older people. Therefore, subsequent studies are needed to totally validate or not a relationship between these two malfunctions.

Finally, it should be concluded that at the present time etiology of CSH remains unknown. It seems that it is unlikely that only one site of the reflex arc is responsible to explain CSH. May be a future direction should be followed with the investigation of associated defects incorporating multiple contributing factors such as sternocleidomastoid muscle denervation and carotid sinus stiffness.

15.3 Carotid Sinus Hypersensitivity and Carotid Sinus Syndrome

When patients with CSH have spontaneous syncope, they are only diagnosed to have carotid sinus syndrome (CSS) if CSM reproduces the spontaneous symptoms (see below). In that case it is generally considered that CSS is responsible for the spontaneous syncope [11, 12].

15.3.1 Cause and Effect Relationship Between Carotid Sinus Massage and Syncope

This relationship seems very likely when the spontaneous syncope occurs during an inadvertent compression or a massage of the carotid sinus, for example when turning the head particularly in the presence of tight collars. This is also true in patients with neck tumors, or after neck surgery or irradiation. However, these patients represent only a minority of those with CSS. It seems more challenging to incriminate CSS as the cause of spontaneous syncope in the absence of the above-mentioned situations. However, there are at least two arguments in favor of the responsibility of CSS to induce spontaneous syncope even in the absence of evident local trigger of the reflex. The first was a pre–post comparison of the recurrence rate of syncope after pacing. Non-randomized studies demonstrated fewer recurrences in patients implanted with a pacemaker than in patients without pacemaker. These results were confirmed by randomized trials [13, 14]. The second argument was based on the recording of spontaneous asystolic episodes by an implanted device in patients with cardioinhibitory response to CSM. In the trials that used this methodology, long cardiac pauses were very commonly registered [15, 16]. These results suggest that a positive response to CSM (see below) in patients with syncope of unknown origin, even in the absence of evident local trigger of the reflex, is highly predictive of the occurrence of spontaneous asystolic episodes.

15.3.2 Epidemiology of CSS

Incidence of CSS in the general population, even restricted to its cardioinhibitory component, remains largely unknown. Its prevalence has been estimated to be <4% in patients <40 years and 41% in those >80 years attending a syncope management clinic/unit [14, 17]. In 1855 consecutive patients >40 years of age with unexplained syncope after the initial evaluation, 164 (8.8%) were considered to have CSS [18]. Of these 164 patients 81% had asystole and 19% vasodepression. In a well-designed multicenter study CSM, indicated after initial evaluation in 73% of 700 patients, was diagnostic in 12% [19]. However, in patients admitted for syncope in general hospitals, the incidence of CSS varies widely from 1% to 60% [20]. These important discrepancies have at least two explanations: in some hospitals CSM is not or only infrequently performed [20] and when performed the methodology varies from one center to another and is not always in accordance with the recommended protocol [21].

15.4 Diagnosis of Carotid Sinus Syndrome

As above-mentioned the diagnosis of CSS needs two conditions: occurrence of spontaneous syncope compatible with a reflex mechanism (this could be obtained by a well-conducted history taking), and a “positive CSM” performed with a precise methodology as described in the practice guidelines and summarized below.

15.4.1 Methodology of CSM

The protocol of CSM has been precisely described in the recently published guidelines of the European Society of Cardiology [21]. The massage is applied in a patient supine with the face rotated contralaterally to the carotid vessel being massaged under continuous ECG and non-invasive beat-to-beat BP monitoring. The site of the maximum carotid pulse is located between the angle of the jaw and the cricoid cartilage on the anterior margin of the sternocleidomastoid muscle. At this site the carotid is gently compressed with an up and down motion with the tips of the second, third, and fourth fingers for a maximum of 10 s to allow symptoms to develop. Then the massage, if negative, is repeated for the same duration on the other side. Thereafter, if needed, it can be repeated with patient, supine, and then in an upright position for both sides. The delay between massages has to be long enough to allow heart rate and blood pressure values to return to baseline.

As noted earlier, the massage is considered positive for CSH in case of ventricular pause lasting >3 s associated or a fall in systolic BP>50 mmHg; however, these objective modifications should be associated with the reproduction of spontaneous clinical

symptoms (syncope or at least pre syncope) to consider the massage “positive” for the diagnosis of CSS. If an asystolic pause is induced by CSM, the vasodepressor component may be hidden, and it could of interest for therapeutic and prospective implications to unmask this potential vasodepressor response. To assess the isolated contribution of depressed BP, CSM is repeated after intravenous administration of 0.02 mg/kg of atropine which eliminates vagally induced asystolic pauses, thereby unmasking vasodepressor response. A positive CSM could be classified under three different forms. The vasodepressor form is defined when CSM reproduces symptoms with an isolated fall (absence of asystole) in systolic BP during at least one massage. The mixed form is diagnosed when symptoms persist after the elimination of baseline asystole by means of atropine. The cardioinhibitory form is diagnosed when symptoms are associated with a long cardiac pause after exclusion of vasodepression.

Finally, it should be stressed once again that CSS can only be established when spontaneous symptoms are reproduced in the presence of bradycardia (this usually requires a pause >6 s) and/or marked hypotension.

15.4.2 Complications of CSM

Carotid sinus massage (CSM) is very well tolerated by the patients and complications are very uncommon. As expected the main potential complications are neurological. Complications of CSM were analyzed in 7319 patients recruited in three studies and neurological complications were observed in only 21 (0.29%). Furthermore, in some of these 21 patients the responsibility of CSM is speculative as the event occurred several hours after the massage. Although there are no precise data to support this recommendation it seems reasonable to avoid CSM in patients with definite TIA or stroke history within the past 3 months and in patients with known carotid artery stenosis.

15.5 Conclusion

It seems well-established that in some patients, mostly older males, the reflex arc beginning in the carotid baroreceptors is impaired resulting in an “excessive” response. The precise physiopathology of this causing increased this abnormal responsiveness remains unknown. Nonetheless, that this abnormality may be responsible for the occurrence of spontaneous syncope in some patients seems well documented. CSM is the diagnostic method used to reveal this abnormality and should therefore be undertaken as part of the syncope evaluation in selected patients (typically older males) with syncope of unknown origin after the initial evaluation.

Conflict of interest None reported

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Chapter 16

Electrophysiology Testing: Appropriate Indications in TLOC/Collapse



Dan Sorajja

16.1 Introduction

When arrhythmias are the cause of a syncopal event, documentation of the responsible arrhythmia has become easier due to the various options of monitoring including inpatient and outpatient cardiac monitors. In one meta-analysis, an implantable cardiac monitor had almost 3.7 times the diagnostic yield as did conventional testing which included external loop recorder, tilt table testing, and electrophysiology study (EPS) [1]. However, some patients have very infrequent symptomatic episodes or are unable to trigger a recording device, and so the ability to correlate an arrhythmia to a syncopal event may be difficult [2]. In these situations, an electrophysiological study (EPS) continues to have a role in the evaluation of syncope.

Certainly, the utility of EPS has diminished over time, partly due to improved monitoring techniques and partly from fewer indications, such as the EPS no longer being required for certain implantable cardioverter-defibrillator (ICD) indications for primary prevention of sudden cardiac death. Registry data shows that only 3% of patients with unexplained syncope undergo EPS after evaluation by cardiologists [3].

An EPS is useful, though, particularly when the clinical situation is suspicious for an arrhythmic cause of the syncope. In some instances, EPS may induce an arrhythmia during which the patient has reproducible loss of consciousness. In other circumstances, EPS may reveal conduction system issues, which may provide a plausible explanation for a prior syncopal event. In particular for patients with underlying structural heart disease or abnormalities on ECG, an EPS may provide valuable information that could alter a patient's care.

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Table 16.1 Indications for electrophysiology study in patients with syncope [1, 24]

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- Class I, B: In patients with syncope and previous myocardial infarction or other scar-related conditions, EPS is indicated when syncope remains unexplained after non-invasive evaluation [1]
 - Class IIa, B-NR: EPS can be useful for evaluation of selected patients with syncope of suspected arrhythmic etiology [24]
 - Class IIa, B-NR: EPS is reasonable in patients with moderate or severe adult congenital heart disease and unexplained syncope [24]
 - Class IIa, B-NR: EPS is reasonable in patients with cardiac sarcoidosis and syncope of suspected arrhythmic etiology [24]
 - Class IIa, B: In patients with syncope and bifascicular bundle branch block, EPS should be considered when syncope remains unexplained after non-invasive evaluation [1]
 - Class IIb, B-NR: Invasive EPS may be considered in patients with Brugada ECG pattern and syncope of suspected arrhythmic etiology [24]
 - Class IIb, B: In patients with syncope and asymptomatic sinus bradycardia, EPS may be considered in a few instances when non-invasive tests (e.g., ECG monitoring) have failed to show a correlation between syncope and bradycardia [1]
 - Class IIb, C: In patients with syncope preceded by sudden and brief palpitations, EPS may be considered when syncope remains unexplained after non-invasive evaluation [1]
 - Class III: No benefit, B-NR: EPS is not recommended for syncope evaluation in patients with a normal ECG and normal cardiac structure and function, unless an arrhythmic etiology is suspected [24]
 - Class III: Harm, B-NR: EPS should not be performed in patients with early repolarization pattern and history of syncope in the absence of other indications [24]
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16.2 EPS Indications in Syncope

Indications for EPS in the evaluation of syncope/collapse are listed in Table 16.1. The EPS can be useful after the initial evaluation of syncope, including a careful history, physical examination, and electrocardiogram (ECG), is non-diagnostic. In obtaining a history, usually the precipitating circumstances give the biggest clue for the etiology.

The utility of EPS in evaluation of syncope depends of the pretest probability of an arrhythmic etiology, which accounts for 14% of syncope [4]. By history, an arrhythmic cause for syncope can occur in any body position, including lying down, and in that case there is frequently little to no prodrome. Cardiac syncope is also suggested when the syncope occurs during exertion. Palpitations may be present, but are usually brief and are not specific (as they may occur with reflex syncope as well). Additional history that could suggest an arrhythmia includes prior ischemic heart disease, depressed left ventricular ejection fraction, prior pacemaker or ICD implantation, or a family history of inheritable cardiac conditions. Findings that increase the likelihood of an arrhythmic etiology include an abnormal ECG and structurally abnormal hearts.

A 12-lead ECG should be performed in the initial evaluation of all patients with syncope. Of note, many ECGs will be unremarkable since patients are frequently asymptomatic at the time of evaluation. On occasion, demonstrative findings to explain the syncope can be found, such as significant pauses, conduction blocks, or tachyarrhythmias. Other disease processes may also have diagnostic ECG features,

Table 16.2 ECG abnormalities suggesting syncope due to arrhythmia

– Bradycardia (excluding from increased vagal tone or medication effect) with heart rates less than 40 beats/min
– Sinus pauses greater than 3 s while awake in non-athletes
– Bundle branch block (particularly alternating left and right bundle branch block) or bifascicular block
– Second-degree AV block Mobitz type II
– High-grade conduction block
– Third-degree AV block
– Supraventricular tachycardia
– Frequent premature ventricular complexes
– Ventricular tachycardia (non-sustained or sustained)
– Pre-excitation
– Brugada type 1 pattern
– Prolonged QT interval or short QT interval
– Epsilon waves or T-wave inversion in right precordial leads suggesting arrhythmogenic right ventricular cardiomyopathy
– Left ventricular hypertrophy (particularly suggesting hypertrophy cardiomyopathy)
– Q waves or myocardial infarction patterns
– Pacemaker or ICD malfunction, particularly with cardiac pauses

such as channelopathies, including long QT syndrome or Brugada syndrome, structural heart diseases, such as hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy, or accessory pathway conduction.

In several risk score systems that evaluate short-term and long-term risk for patients seen in outpatient or emergency department scenarios, the definition of abnormal ECG typically includes any rhythm other than sinus rhythm, bundle branch blocks, second-degree AV block type 2, high-grade AV block, complete heart block, Q waves, significant ST changes, or prolonged QT interval [5–12]. A list of ECG abnormalities suggesting an arrhythmic etiology for syncope is compiled in Table 16.2.

The label of structurally abnormal hearts includes cardiomyopathy, valvular heart disease, or conduction system issues [13]. In the presence of these findings, the diagnostic yield of EPS was approximately 41%, with 21% having inducible ventricular tachycardia (VT) and 34% having bradycardia [14], although these data are quite old and reflect a different era. For patients with ischemic or non-ischemic cardiomyopathy, syncope of undetermined etiology should be concerning for an arrhythmic etiology, and these patients may benefit from goal-directed medical therapy and consideration of ICD therapy.

One caveat is that the presence of an arrhythmia does not necessarily mean it is the etiology of syncope. Young patients may have bradycardia from enhanced vagal tone, but with no causal relation to their syncope. Similarly, supraventricular tachycardia (SVT) infrequently causes syncope, but older patients are more likely to have presyncope or syncope with SVT than are younger individuals. For atrial fibrillation with rapid ventricular response, syncope is unlikely unless there are post-conversion pauses that are significant. In one series looking at ICD therapies, approximately 9% have syncope during sustained monomorphic VT [15].

Much of the data supporting EPS as a diagnostic tool are from referral centers, where there is a high pretest probability of an arrhythmia. When patients have syncope in the setting of a normal ECG and a structurally normal heart, EPS is usually unhelpful, with the yield ranging from 2.6 to 10% [14, 16].

16.3 EPS Techniques

The setup for an EPS should include multi-electrode catheters positioned within the heart to identify what arrhythmia, if any, could explain the syncope. Usually, the minimum setup would include catheters placed at the high right atrium (HRA), His bundle area, and right ventricle (RV). Occasionally a coronary sinus (CS) catheter can also be used to reveal left atrial electrograms and for stimulation purposes (Fig. 16.1). In addition, for some patients, arterial access should be obtained to monitor the hemodynamic consequences of an induced arrhythmia. Arterial access can also be used to retrogradely access the left ventricle for recording from and stimulate this chamber. Uncommonly, EPS with the patient tilted head-up may be useful [17].

For the HRA, the catheter should be positioned near the sinus node region. The RV catheter can be placed in the apex but may require repositioning at the base for certain pacing maneuvers.

16.4 Basic Electrophysiology Study Protocol for Evaluation of Syncope

The electrophysiology study should include the baseline measurements as listed in Table 16.3. The stimulation protocol is designed to assess the robustness of the conduction system, and the inducibility and tolerance to observed arrhythmias. The basic EPS protocol should include the maneuvers as listed in Table 16.4.

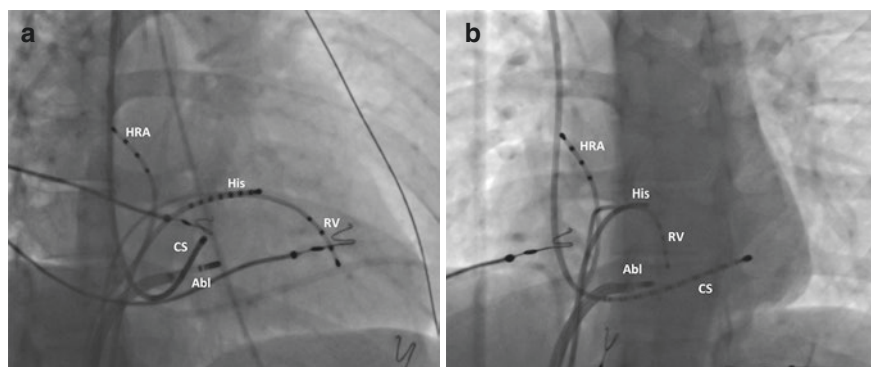


Fig. 16.1 Catheter positions for an electrophysiology study. Catheter positions during a case for typical atrioventricular nodal reentrant tachycardia. (a) The catheter positions in fluoroscopic right anterior oblique view. (b) The catheter positions in fluoroscopic left anterior oblique view. HRA high right atrium, RV right ventricle, CS coronary sinus, Abl ablation catheter

Table 16.3 Baseline diagnostic EPS measurements

– Ventricular cycle length (RR interval): time between subsequent ventricular signals on the surface ECG and on an intracardiac catheter. This timing represents the heart rate
– PA interval: time from the earliest atrial activation (which may be seen on the surface ECG, HRA catheter, or CS catheter) to the atrial electrogram on the His bundle catheter. Prolongation in this interval suggests intra-atrial conduction issues
– AH interval: time from the atrial electrogram to the His electrogram on the His bundle catheter. This interval represents the time between the atrial signal arriving at the tissue adjacent to the AV node then emerging at the His bundle. The timing is susceptible to a variety of factors, particularly autonomic tone
– HV interval: time from the earliest His electrogram on the His bundle catheter to the earliest ventricular activation (which may be seen at the surface ECG, RV catheter, or the His bundle catheter). The HV interval is a measurement of conduction from the His bundle through the Purkinje system
– QRS duration: duration of ventricular activation by surface ECG
– QT interval: duration of ventricular activation and repolarization by surface ECG

Table 16.4 Basic electrophysiology study protocol

– Assessment of sinus node function by sinus node recovery time (SNRT) and corrected sinus node recovery time (cSNRT)
– Assessment of His-Purkinje system by measurement of HV interval in response to burst atrial pacing and atrial extrastimuli
– Assessment of inducibility of supraventricular arrhythmias by programmed electrical stimulation including decremental atrial burst pacing and up to two extrastimuli at two drive cycle lengths
– Assessment of inducibility of ventricular arrhythmias by programmed electrical stimulation including decremental ventricular burst pacing and up to two extrastimuli at two drive cycle lengths
– Pharmacologic challenge should be considered. If the HV interval is indeterminate, procainamide 10 mg/kg or ajmaline 1 mg/kg can be used. In cases with clinical suspicion of SVT, isoproterenol 0.01–0.04 mcg/kg/min or atropine 0.5–1 mg can be used. For ventricular arrhythmias, isoproterenol can be used at similar doses as SVT cases

16.5 Assessment of Sinus Node Dysfunction

Sinus node dysfunction can manifest in a number of presentations (Fig. 16.2): sinus bradycardia, sinus arrhythmia, sinus pauses and arrest, tachy-brady syndrome, atrial standstill, and chronotropic incompetence. Correlation of symptoms to the presentation of sinus node dysfunction usually requires ambulatory monitoring. To increase the yield of monitoring, its duration should be commensurate with the expected frequency of episodes.

When a correlation can be established between sinus node dysfunction and symptoms, the consensus would be to perform a permanent pacemaker implantation, which is effective for symptom relief [1]. The issue is that many patients have very limited recurrences or significant harm with prior episodes. In some patients, a permanent pacemaker may still be reasonable if patients have asymptomatic pauses or intrinsic sinus disease [1]. For other patients, more information is needed, and as such, EPS evaluation of sinus node dysfunction can be valuable in suspected cases



Fig. 16.2 Examples of sinus node dysfunction. (a) Holter monitoring showing sinoatrial exit block Mobitz type 2, for which the patient was symptomatic. (b) Monitoring showing spontaneous termination of atrial fibrillation with an asystolic pause of 10.8 s (6 s not shown) before a junctional escape rhythm occurs

of syncope due to arrhythmic causes. When patients have asymptomatic sinus bradycardia, such as heart rates less than 50 beats/min or sinoatrial block, the pretest probability of syncope from bradycardia is elevated.

In evaluating sinus node function, the measurements of interest include the sinus node recovery time (SNRT) and sinoatrial conduction time (SACT). These have a sensitivity and specificity of 68% and 88%, respectively, when used together to detect sinus node dysfunction [18].

During evaluation of SNRT, testing takes advantage of the spontaneous automaticity of the sinus node and the concept of overdrive suppression. Overdrive suppression of the sinus node is accomplished by atrial pacing, for 30–60 s at a rate faster than the baseline sinus rate. This test is performed at two or more pacing cycle lengths, usually starting at a cycle length 20 ms shorter than the baseline sinus rate. After cessation of pacing, SNRT is the time between termination of high right atrial pacing and the spontaneous return of sinus node activity. Due to the influences of

multiple factors such as autonomic tone and the sinus rate itself on SNRT, the SNRT is corrected for the pre-pacing baseline cycle length. The corrected SNRT (cSNRT) is measured by subtracting the baseline sinus cycle length from the SNRT.

$$\text{Corrected SNRT (cSNRT)} = \text{SNRT} - \text{baseline sinus cycle length}$$

SNRT usually reaches a maximum duration at pacing cycle lengths between 400 and 500 ms. Values greater than 1600 ms for SNRT or 525 ms for cSNRT are deemed abnormal (Fig. 16.3). These findings have a sensitivity of 50–80% and specificity of >95% for detection of sinus node dysfunction. With longer cSNRT,

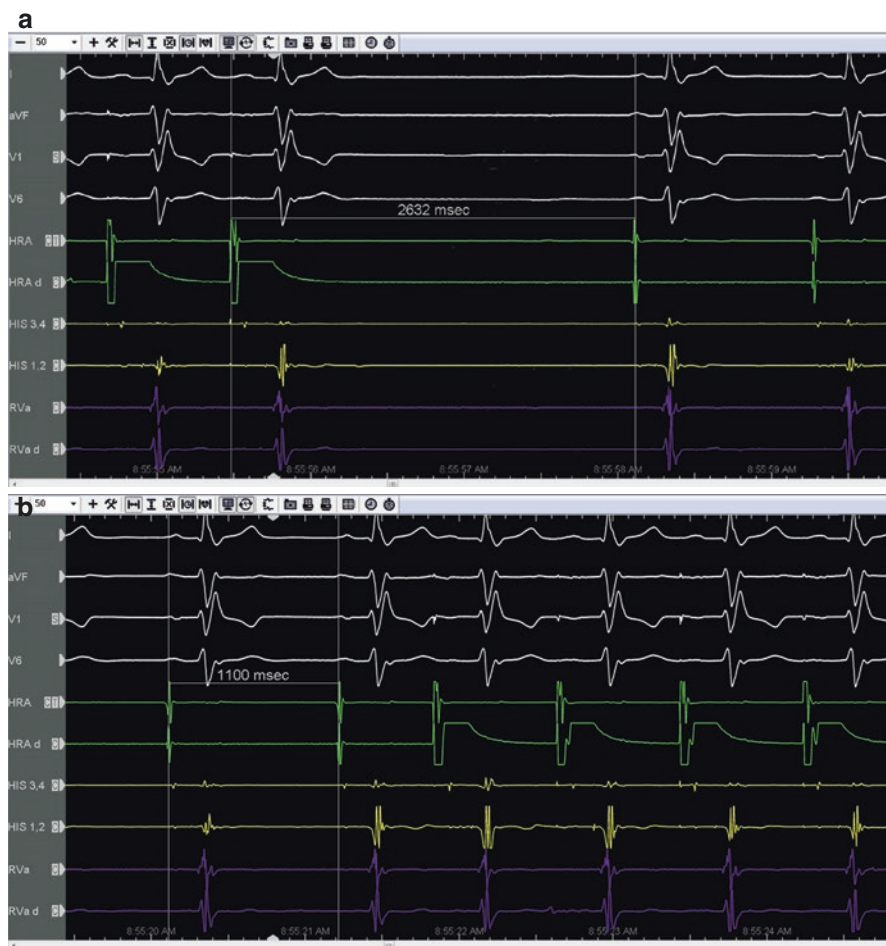


Fig. 16.3 Abnormal sinus node recovery time (SNRT). (a) After cessation of overdrive suppression of the sinus node for 30 s, the sinus node activity spontaneously returns after 2632 ms. (b) The sinus node rate prior to the pacing was 1100 ms, so the corrected SNRT is 532 ms

such as ≥ 800 ms, the risk of syncope is eight times higher [19] than when the cSNRT is less than this cutoff. When the SNRT is greater than 2 s, or the cSNRT is greater than 1 s, then sinus node dysfunction is the probable cause of syncope after other etiologies are ruled out [20]. For patients with a prolonged cSNRT and history of syncope and asymptomatic sinus bradycardia, a permanent pacemaker should be considered [1]. It should be noted that despite pacing in patients with sinus node dysfunction, there is frequent recurrence, approximately 25% over 5 years, due to many patients also having a vasodepressor reflex mechanism with sinus node disease [1].

Two main methods, as described by Strauss et al. and Narula et al. [21, 22], are typically used to evaluate SACT. With the Strauss method [22], premature atrial complexes are introduced from the HRA catheter after a “drive train” of typically 8 sinus beats. The premature atrial complexes are advanced progressively earlier in 5–10 ms increments, until the whole atrial diastolic period is scanned. When the premature atrial complexes result in an earlier sinus node beat without a full compensatory pause, the premature atrial complex is in the zone of reset. In this zone, two sinus cycle lengths will be longer than the time between two HRA activations that encompass the PAC. Theoretically, the time between the PAC from the HRA catheter and then the return activation in the HRA catheter represents the sinus cycle length plus the conduction time into and out of the sinus node. As such, the SACT is the time between the PAC and sinus activation return seen in the HRA catheter divided by two.

For the Narula method [21], atrial pacing is performed at a rate slightly faster than the observed sinus rate (≤ 10 beats/min faster) for an 8 beat drive. With cessation of pacing, the subsequent 8 or more spontaneous sinus node cycles are analyzed. The atrial pacing procedure is repeated 4 or 5 times at the same pacing cycle length. The SACT conduction is the interval between the last paced atrial electrogram and the atrial electrogram of the escape sinus node cycle, then subtracting the mean sinus cycle length. Assuming there is no suppression of automaticity, this interval represents the conduction time into and out of the sinus node. Usually the SACT using the Narula method is more easily performed since some patients do not have a zone of reset that can be observed. Another difference is the Narula SACT is usually shorter than the Strauss method, ranging from 2 to 77 ms in the original study, but with a coefficient of correlation of $r = 0.97$ between the 2 methods.

Apart from SNRT and SACT, sinus node function can also be assessed by determining the intrinsic heart rate, which is on a measure of sinus node automaticity. The predicted intrinsic heart rate is shown below [23].

$$\text{Intrinsic heart rate (in beats per minute)} = 118 - (0.57 \times \text{age in years})$$

By combining beta-blocker and anticholinergic medications such as propranolol 0.2 mg/kg and atropine 0.04 mg/kg, autonomic influence on the heart rate is essentially removed. If the resting heart rate is lower than the expected intrinsic heart rate after beta-blocker and anticholinergic challenge, then vagal tone is



Fig. 16.4 Spontaneous AV block greater than 3 s

likely predominant over sympathetic tone. This can be confirmed by giving atropine 1 mg IV and witnessing a heart rate increase of greater than 20 beats/min. If the abnormally low intrinsic heart rate does not increase or respond to atropine, this would be consistent with sick sinus syndrome [23].

16.5.1 EPS and Conduction System Disease

Conduction system disease, particularly AV block (Fig. 16.4), should be considered and evaluated in patients whose history is consistent with a cardiac cause of syncope. These patients can have syncope in any body position, including lying down, and they frequently have little to no prodrome. For evaluation in patients with recurrent episodes of syncope, ambulatory external cardiac monitoring should be prescribed with the duration commensurate with the frequency of recurrence. For patients with unknown recurrence or less frequently than monthly, an implantable loop recorder should be considered [1, 24].

For patients with suspected conduction system disease, an EPS is useful when monitoring is unable to document a symptomatic event or if monitoring may be not feasible. EPS takes advantage of the different properties of the conduction system, specifically whether there is an issue in the AV node or distal to the AV node in the intrinsic His-Purkinje cardiac conduction system (Table 16.5). The determination is clinically important since the AV node has automaticity, or spontaneous depolarization, providing a more stable escape rhythm than the His-Purkinje system and ventricular myocytes both of which typically do not display automaticity under normal conditions. There are clues on ECG or rhythm strips that suggest localization of block to the AV node, and these include presence of PR interval greater than 300 ms, a narrow QRS complex, and second-degree AV block Mobitz type 1. AV block localizing distal to the AV node may have a wide QRS complex or second-degree AV block Mobitz type 2.

During the EPS, a prolonged His duration or split His is consistent with intra-Hisian conduction disease, while a prolonged HV interval is consistent with intra- or infra-His conduction problems, and carries a higher risk of the patient developing AV block

Table 16.5 ECG findings suggesting block at the AV node versus distal to the AV node*AV node conduction issue*

- Grouped beating
- Longer conducted PR intervals
- Narrow QRS duration
- Heart rate increases with exercise
- Heart rate increases with atropine
- Heart rate decreases with carotid sinus massage

Infra-nodal conduction issue

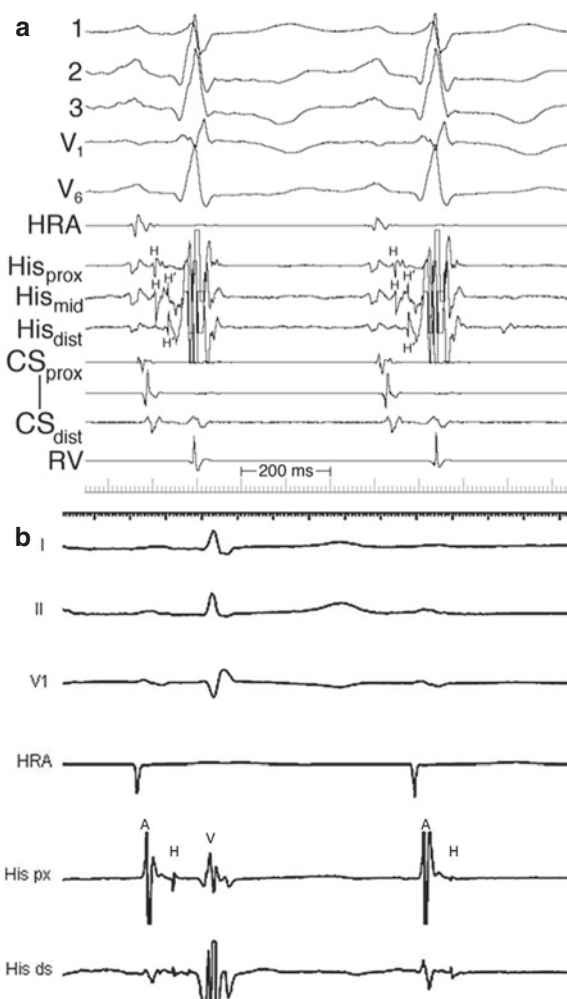
- Not grouped beating
- Shorter conducted PR intervals
- Bundle branch block or wide QRS
- Heart rate decreases with exercise
- Heart rate decreases with atropine
- Heart rate increases with carotid sinus massage

Fig. 16.5 Intra- and

Infra-Hisian disease.

(a) A split His is observed consistent with intra-Hisian disease. (b)

Infra-Hisian disease is seen with the atrial and His electrograms without ventricular activation



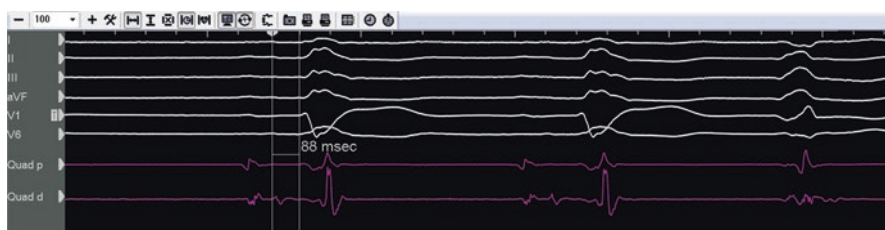


Fig. 16.6 Baseline HV greater than 70 ms

(Fig. 16.5). With a normal HV interval or a slightly prolonged HV interval (<60 ms), the risk of progression to AV block is low, approximately 2–5%. In one report by Scheinman et al. [25], none of the patients with normal HV developed AV block in follow-up, while 26% of those patients with $HV \geq 70$ ms developed AV block (Fig. 16.6). In another series, a prolonged HV interval carried a 28% risk of AV block over 7 years [26]. As such, with similar data from other series, a prolonged HV interval ≥ 70 ms is predictive of future AV block.

Pharmacologic challenge with a sodium channel blocker such as procainamide, ajmaline, or disopyramide can be used to increase the yield of the EPS when the HV interval is mildly prolonged. If the HV interval significantly prolongs to >100 ms, there is second-degree AV block Mobitz type 2, high-degree AV block, or complete heart block, then approximately two-thirds of these patients go on to have spontaneous AV block in follow-up over 5 years [27, 28].

A special consideration is patients with syncope in the setting of bundle branch block which requires consideration of other factors. In the guidelines, syncope with a bundle branch block qualifies a patient to be a candidate for pacing support. Right bundle branch block with left anterior fascicular block is the most common ECG pattern preceding complete heart block [29]. In patients with bundle branch block and unexplained syncope, a permanent pacemaker is indicated when the HV interval is ≥ 70 ms [30, 31]. Some of the patients, those with bradycardia or conduction block, particularly benefit as these patients have a higher risk of progression to AV block [32]. An empiric pacemaker has less benefit if applied to all patients with bifascicular block and unexplained syncope [33]. In addition, patients with bundle branch block carry a higher incidence of ventricular arrhythmias and sudden cardiac death. There are patients who have inducible ventricular arrhythmias as the etiology of their syncope [34–37]. The inducibility of ventricular arrhythmias in evaluating bundle branch block should be taken within the context of the patient's comorbidities, which frequently will also include low left ventricular ejection fraction and prior myocardial infarction. The ventricular arrhythmias from programmed stimulation may not identify who is at increased risk of death, and these patients may be candidates for an ICD for cardiac resynchronization device [35, 36]. In addition, among those patients with syncope and bundle branch block, there will be a large percentage of

them with vasovagal syncope, and many of these patients may not derive benefit from a pacemaker if their predominant manifestation is vasodepressor type syncope.

With programmed stimulation, decremental atrial pacing may show intra- or infra-His block in less than 5% of cases, but can predict AV block. When the HV prolongs by >10 ms or second-degree AV block occurs, in approximately 5–6% of cases, these patients go on to develop complete heart block in 40% of cases over 42 months of follow-up [27]. Otherwise if 2nd-degree Mobitz type 2 (infra-Hisian) or 3rd-degree block is seen with decremental atrial pacing or with pharmacologic challenge, a permanent pacemaker is indicated when these patients have a history of syncope and bifascicular block [1]. When permanent pacemaker is implanted for treatment of 2nd or 3rd-degree AV block, the rate of syncope has been previously shown to decrease to 1–3.4% over 5-year follow-up [38, 39].

During atrial extrastimuli, signs of intra-Hisian disease include a His duration >30 ms or having a split configuration. Intra- or infra-Hisian disease could be suggested by loss of AV conduction during atrial extrastimuli at a coupling interval <350 ms [40, 41].

16.5.2 Supraventricular Tachycardia

SVT is an uncommon cause of syncope, being responsible for approximately 2% of cases [4]. However, in patients without structural heart disease, SVT, particularly when the rate is greater than 160 beats/min for greater than 32 beats, should be considered as the cause (Fig. 16.7) [42–44]. While younger patients may have more

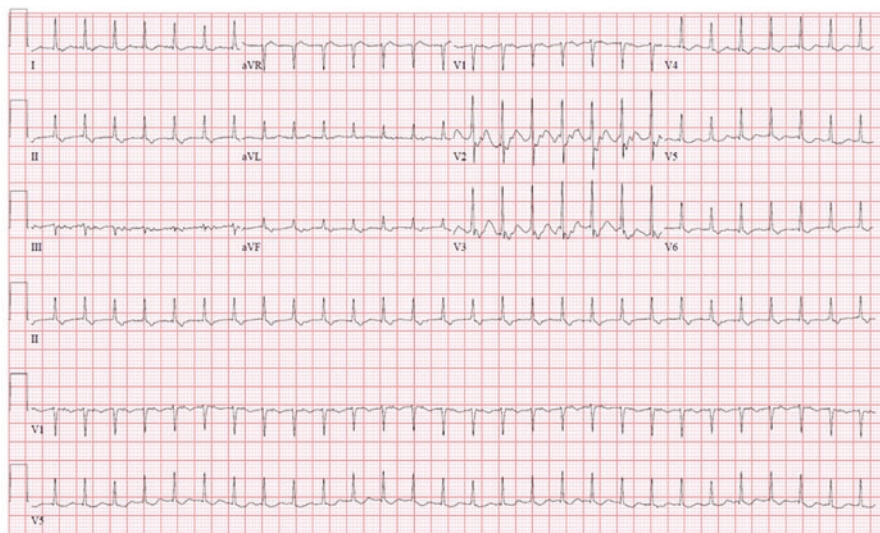


Fig. 16.7 Rapid supraventricular tachycardia greater than 160 beats/min. This case of orthodromic atrioventricular reentrant tachycardia had a rate of 170 beats/min

rapid SVT, older patients are more prone to presyncope or syncope during episodes. The symptoms of palpitations and lightheadedness likely are independent of the rate, but the symptom burden could be related to the degree in which the SVT rate exceeds the predicted maximal heart rate for a patient. Of note, palpitations and lightheadedness are non-specific, and can precede vasovagal physiology as well as VT. Patients with paroxysmal atrial fibrillation may also have a concomitant abnormal autonomic response, which may trigger vasovagal syncope with onset of atrial fibrillation [45]. In addition, the palpitations and lightheadedness could be related to sinus node dysfunction or significant pauses before sinus rhythm resumes, such as after termination of atrial fibrillation. For patients with congenital heart disease such as Fontan, Ebstein anomaly, tetralogy of Fallot, prior Mustard, prior Senning, atrial arrhythmias can be responsible for syncope [24].

For the EPS, the setup is quite important. As noted above, the catheters should include one at the HRA, His bundle, and right ventricle. Strong consideration should be given to arterial blood pressure monitoring which can provide a quick reference for determining hemodynamic tolerance to any induced arrhythmia. In addition, placement of a CS catheter should be considered as it can be helpful for determining activation sequences and for left-sided stimulation as well. Programmed stimulation should be performed with the patient on minimal if any sedation, as it may suppress arrhythmias as well. The programmed stimulation should include decremental atrial burst pacing and up to two extrastimuli at two drive cycle lengths. If there are no inducible arrhythmias, isoproterenol 0.01–0.04 mcg/kg/min or atropine 0.5–1 mg can be used, followed by repetition of the pacing protocol during the medication effect and washout phase of it.

16.5.3 *Ventricular Tachycardia*

Ventricular tachyarrhythmias comprise approximately 3.8% of cases of syncope [4]. The higher incidence of syncope with ventricular tachyarrhythmias likely is related to the more frequent presence of structural heart disease and diminished left ventricular function in these patients. However, structural normal hearts can present with ventricular tachyarrhythmias, including fascicular VT and idiopathic VT, which can originate from the right ventricular outflow tract, aortic cusps, left ventricular summit, tricuspid annulus, mitral annulus, crux, and papillary muscles [46, 47]. Congenital channelopathies, such as those from long QT syndromes, Brugada syndrome, and catecholaminergic polymorphic VT, in otherwise structurally normal hearts carry a risk of polymorphic VT.

Of note, the majority of patients with VT do not have syncope with 64–91% remaining conscious during episodes of prior sudden cardiac arrest or sustained monomorphic VT, respectively. Also, if a VT has been documented without loss of consciousness, then it is unlikely to cause syncope with a recurrence [15]. That being stated, if sustained monomorphic VT is induced in a patient with a prior myocardial infarction, the VT is likely the cause of syncope [48]. Ventricular

Table 16.6 Clinical findings that increase the likelihood that ventricular tachycardia as the cause of syncope

- Ventricular arrhythmia rate ≥ 200 beats/min
- Prior history of sustained monomorphic ventricular tachycardia
- Coronary artery disease, particularly history of myocardial infarction
- Structural heart disease (hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, sarcoidosis)
- Depressed left ventricular ejection fraction
- Left ventricular hypertrophy
- Prior cardiac surgery for congenital anomalies, revascularization, valve replacement or repair, tumor removal
- ECG evidence of long QT syndrome, short QT syndrome, or Brugada syndrome
- Abnormal signal-averaged electrocardiogram (SAECG) or T-wave alternans study
- Advanced age

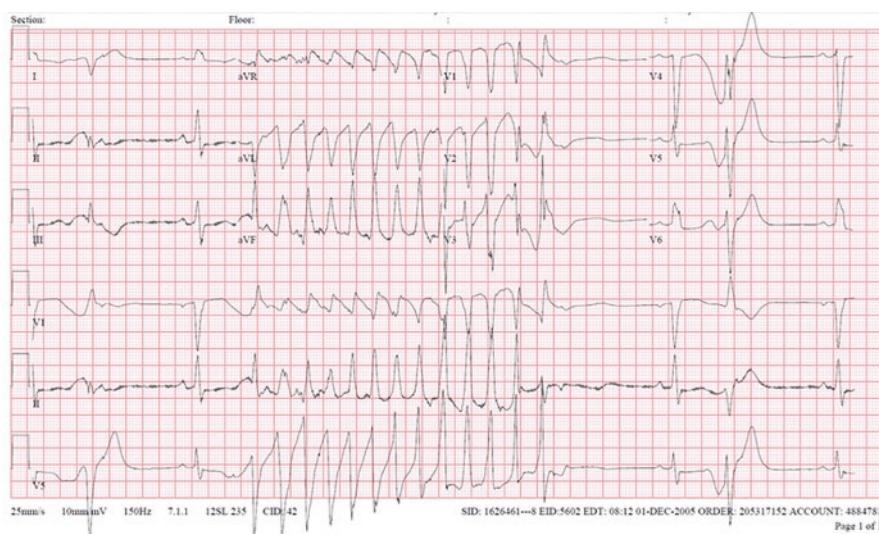


Fig. 16.8 Paroxysmal rapid ventricular tachycardia. In this patient with prior syncope, His ECG captured non-sustained ventricular tachycardia with a ventricular rate of 215 beats/min reproducing his symptoms

fibrillation is more non-specific and may be more so a product of aggressive pacing [49].

The mechanism of syncope during a ventricular arrhythmia varies, and may have multiple factors playing a role. Ventricular arrhythmias with a rate greater than 200 beats/min carry a 65% incidence of syncope or presyncope, while only 15% of patients with ventricular rates less than 200 beats/min have syncope or presyncope (Fig. 16.8) [50]. In another series, syncope occurred in 58% when the VT had a cycle length shorter than 250 ms [15]. Other factors that potentially explain syncope from ventricular arrhythmias include the ventricular dyssynchrony, change in

autonomic tone, abrupt change in rate, and body position during the arrhythmia [51]. There are factors that suggest ventricular tachyarrhythmias are the cause of syncope. These findings are summarized in Table 16.6.

Some patients may have worrisome substrate that makes them prone to have significant ventricular arrhythmias. EPS would be reasonable in asymptomatic patients with cardiac sarcoidosis as 11% of these patients have inducible sustained ventricular arrhythmias which carry an adverse prognosis [52]. For patients with Brugada ECG pattern and syncope, the value of EPS is controversial, but may be of value in cases where an arrhythmia, rather than vasovagal syncope, is suspected as the cause [53–55]. If VT or ventricular fibrillation can be induced with 1 or 2 ventricular extrastimuli during programmed electrical stimulation, then these patients have a slightly increased risk of arrhythmic events [56]. In patients with early repolarization pattern and history of syncope, an EPS is not recommended as it is unable to differentiate those patients with an increased risk of ventricular fibrillation [57]. Patients with moderate to severe adult congenital heart disease along with syncope, an EPS is reasonable since both monomorphic and polymorphic ventricular tachyarrhythmias occur, particularly with tetralogy of Fallot and transposition of the great arteries [58, 59].

Similar to the setup for SVT, when performing an EPS for evaluation of inducibility of ventricular arrhythmias, catheter setup should include arterial blood pressure monitoring for assessment of hemodynamic tolerance. Minimal, if any, sedation should be used during the programmed electrical stimulation, which should include decremental ventricular burst pacing and up to two extrastimuli at two drive cycle lengths. If there are no inducible arrhythmias, isoproterenol 0.01–0.04 mcg/kg/min can be used, with repeat programmed electrical stimulation performed during isoproterenol effect and during the washout phase.

If a patient has syncope of undetermined etiology and has inducible ventricular arrhythmias that are clinically relevant or significant, then the patient is a candidate for an ICD. Certain cardiac substrates are more prone to significant ventricular arrhythmias. In patients with hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, or sarcoidosis, any significant ventricular arrhythmia in the setting of prior syncope would make these patients a candidate for ICD implantation. An EPS reproduces the clinical arrhythmia in 76% of cases, but often is accompanied by a non-specific atrial or ventricular arrhythmia [60]. However, determination regarding the clinical significance of any induced arrhythmia requires perspective. If a patient has had a prior myocardial infarction, then any induced ventricular arrhythmia is more likely to be the cause of syncope, whereas VT has a lower predictive value in non-ischemic cardiomyopathy. ICD therapy remains a reasonable therapy in these non-ischemic cardiomyopathy patients when they have significant LV dysfunction and unexplained syncope [60–62]. In addition, inducible ventricular tachyarrhythmias that require aggressive stimulation protocols (such as triple ventricular extrastimuli in the setting of isoproterenol infusion) are less specific (Fig. 16.9). If there is no inducible sustained monomorphic ventricular tachyarrhythmia, these patients have a better prognosis with lower subsequent risk of VT [63].

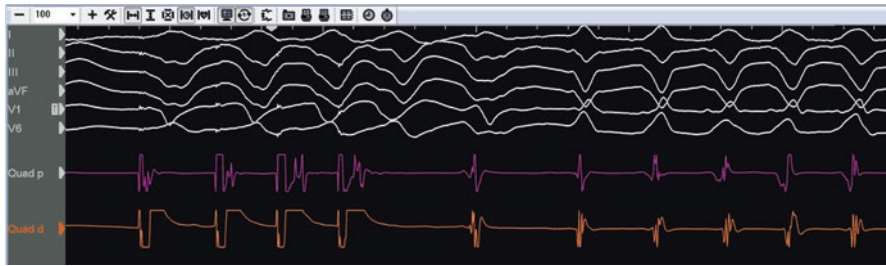


Fig. 16.9 Monomorphic ventricular tachycardia is induced after triple ventricular extrastimuli

Ablation of ventricular arrhythmias is discussed below. For patients that are determined to be candidates for an ICD, it should be noted that an ICD would not prevent syncope. Several studies have shown that even with shorter detection intervals prior to treatment, the time between the arrhythmia and termination by shocking and non-shocking therapy is insufficient to prevent syncope. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), the rates of syncope did not differ between the three treatment arms of ICD versus amiodarone versus placebo [20, 64].

16.5.4 Ablation of Arrhythmias

For any induced arrhythmias, the question is whether the arrhythmia is the clinical one causing syncope, or is at least an arrhythmia suspicious enough to be the culprit arrhythmia. If an SVT has been documented to cause syncope prior to an EPS, anti-arrhythmic medications can be considered before proceeding to an EPS and attempted ablation. If the SVT is induced during an EPS, catheter-based ablation should be considered to address the arrhythmia at the same time as the EPS, since ablation can potentially provide long-term freedom from these arrhythmias. For ventricular tachyarrhythmias that result in syncope, medication is frequently adjunctive therapy to an ICD or need for catheter-based ablation, whether or not structural heart disease is present. Catheter-based ablation can reduce the frequency of ventricular tachyarrhythmia recurrence, thereby reducing syncope recurrence [1, 62].

For patients with an arrhythmic cause of their syncope, an EPS can provide the diagnosis to facilitate potentially curative treatment via catheter-based ablation. Use of radiofrequency or cryothermia energies are the two most common types of energy delivery systems used, but investigative alternative sources such as laser balloon, high-frequency ultrasound, and pulsed electric fields hold potential for therapeutic use in the future [65–67].

For certain arrhythmias, ablation therapy can provide freedom from the arrhythmias exceeding 95% in long-term follow-up such as those related to accessory pathways (orthodromic and antidromic atrioventricular reentrant tachycardia), atrioventricular nodal reentrant tachycardia, and typical atrial flutter. Other arrhythmias such as atrial fibrillation, atypical atrial flutter, atrial tachycardia, idiopathic VT, and reentrant VT can also be ablated with relatively good success.

16.5.5 Inconclusive EPS Despite Suspicion of an Arrhythmic Cause of Syncope

Despite a high pretest probability of an arrhythmic etiology and performing a comprehensive EPS, some EPS are inconclusive. In these situations, a negative EPS is unable to exclude arrhythmic syncope. In these patients, an implantable loop recorder should be considered, as it can provide up to 4 years of monitoring to correlate symptoms to potential arrhythmias. Certain patients, including those with bundle branch block, epilepsy, or unexplained falls, have shown the diagnostic and cost-effective utility of implantable loop recorder monitoring [1]. For suspicion of conduction issues, further ambulatory monitoring or an implantable loop recorder can be considered.

16.6 Conclusion

While the utility of EPS has diminished over time in evaluation of transient loss of consciousness and collapse, EPS remains useful especially when a patient's clinical situation remains suspicious for arrhythmic etiologies. In patients with infrequent recurrences of symptoms or loss of consciousness, or inability to trigger ECG-type monitoring devices, an EPS with its findings can potentially explain the underlying cause of syncope, even after an exhaustive non-invasive evaluation.

Conflicts of Interest US patent 10369357: Percutaneous temporary epicardial pacemaker system.

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Chapter 17

The Syncope Evaluation Unit: Essential Features, Current Status



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17.1 Epidemiology and Current Practice

Syncope is common in the general population. The incidence depends on the population being evaluated. Studies of syncope report prevalence rates between 15% and 39% with recurrent syncope occurring in approximately 13.5% of patients [1]. The first episode presents in a bimodal distribution with a high incidence in patients between the ages of 10 and 30 years, relatively uncommon in middle-aged adults, and peaking again in patients older than 65 years [2]. In the Framingham Heart Study, the overall incidence rate of a first report of syncope was 6.2 per 1000 person-years. The incidence rates increased with age, with a prominent rise at 70 years. The 10-year cumulative incidence was 6% [3]. In a cross section of 1925 randomly selected residents from Olmsted County, Minnesota, age 45 years and older, 364 (19%) (median age of 62 years) reported an episode of syncope in their lifetime. The prevalence was much higher in females (22% versus 15%, $P < 0.001$) [4]. While most patients with syncope are evaluated in the outpatient setting, a significant number of patients present to the emergency department (ED). Several reports found that 3–5% of all ED visits and 1–6% of all hospital admissions were due to syncope/collapse [5].

Despite published guidelines, significant variability exists in the approach and management of patients with syncope/collapse. As a result, providers often hospitalize patients, particularly older adults, without a clear cause for syncope/collapse for diagnostic evaluation. Furthermore, there has been overuse of expensive tests such as brain imaging and underuse of inexpensive tests such as detailed medical history

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taking, tilt table testing, and carotid sinus massage. With these practices, the rate of admission has been high and the rate of diagnosis low. Several models of syncope units (SUs) have been established to address this problem and have shown promise.

17.2 Rationale for a Syncope Unit

The goal of establishing a SU is reduction in the rate of unexplained syncope/collapse, rate of hospitalizations and total cost per diagnosis. The European Society of Cardiology (ESC) 2009 guidelines recommended the establishment of formal SUs, being either virtual units or geographically contained, staffed by syncope experts and having access to appropriate diagnostics and therapies. The term “syncope unit” (SU) was defined as a facility featuring a standardized approach to the diagnosis and management of transient loss of consciousness (T-LOC). Unfortunately, despite this recommendation, SUs are not widely established in clinical practice.

When utilizing a standardized approach, the SU has been shown to reduce both under-diagnosis and misdiagnosis of syncope which is estimated to be as high as 40% in the outpatient and emergency department (ED) settings. A dedicated syncope evaluation unit can also help in reducing unnecessary hospitalizations. This is accomplished by performing risk assessment according to recent guidelines (Fig. 17.1). In the Syncope Evaluation in the Emergency Department Study (SEEDS) [6], patients with syncope and intermediate risk were randomized to SU

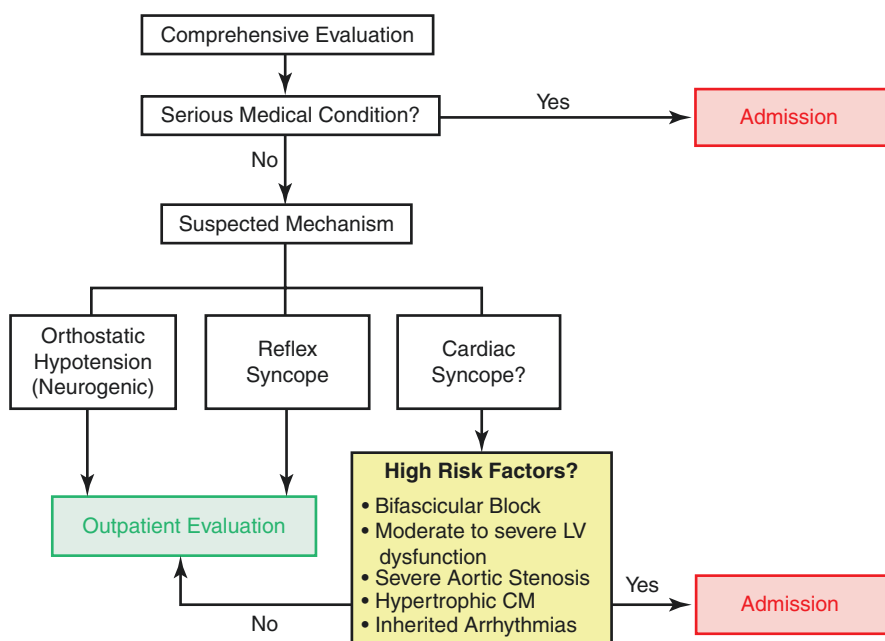


Fig. 17.1 Risk assessment and indications for admission in patients with syncope

evaluation and standard care. When compared to the standard care group, the SU group had a higher rate of diagnosis (67% versus 10%, $p < 0.001$), lower rate of admissions (43% versus 98%, $p < 0.001$), and reduction in total patient-hospital days from 140 to 64. In the ED Observation Syncope Protocol (EDOSP) trial, intermediate-risk older adults presenting to the ED with syncope were randomized to an ED observation syncope protocol or inpatient admission. An ED observation protocol resulted in a lower inpatient admission rate (15% vs. 92%), shorter hospital length-of-stay (29 vs. 47 h), and lower hospital costs than the admission group [7]. Similarly, several other studies involving established SUs have reported decreased cost by reducing the number of admissions, duration of hospital stay, and unnecessary testing along with an increase in the rate of diagnosis [8].

17.3 Essential Requirements for a Syncope Unit

There are a number of essential requirements to consider when establishing a SU (Table 17.1). Key stakeholders should be invited to participate at the initial stages of development and implementation of the unit. The stakeholder group should include hospital/clinic management, referring physicians (e.g., ED, Primary Care, Medical and Surgical Specialists), consultant physicians (e.g., Otolaryngology, Neurology, Psychiatry, Geriatrics), nurses, other allied medical professionals, and patients. Understanding the marketplace is critical when establishing a SU. Identifying the catchment area, current and projected patient volume, clinic location, and referral network is essential.

Table 17.1 Requirements for a syncope unit

Staffing
• One or more providers of any specialty who are syncope specialists
• A team of professionals (physicians, nurse practitioners, specialized nurses) dedicated to syncope patients
Facility and Protocol
• Syncope unit accessible to outpatients, ED, and inpatients
• Internal diagnostic and management protocols agreed by all stakeholders
Equipment and Procedures
• 12-lead ECG
• Ambulatory cardiac monitors (Holter monitor, event monitor, Zio patch, ILR)
• Implantable loop records (with trained staff for implant and monitoring)
• 24-h blood pressure monitoring
• Tilt table with non-invasive beat-to-beat blood pressure monitor
• Basis autonomic function tests
Therapy
• All syncope patients should remain under the care of the SU until the efficacy of therapy has been established
Data
• All medical records should remain within the SU database management system
• Collaborative research possibilities with other SU should be explored

Table 17.2 Tests and assessments available in the syncope unit

<i>Initial Assessment</i>	
<ul style="list-style-type: none">• History and physical exam• 3-minute orthostatic blood pressure measurement• 12-lead ECG	
<i>Subsequent test and assessment (when indicated)</i>	
<ul style="list-style-type: none">• Blood tests (e.g., electrolytes, complete blood count, d-dimer, glucose, etc.)• Provocative tests (tilt table test with or without carotid sinus massage)• Monitoring (Holter monitor, event monitor, Zio patch, ILR)• Autonomic function tests (standing test, Valsalva, maneuvers, deep breathing, or access to other autonomic testing)• Cardiac evaluation (echocardiogram, stress tests, EP study, coronary angiogram)• Neurological evaluation (CT, MRI, EEG, Video EEG)• Geriatric evaluation (cognition, gait and balance, visual, polypharmacy)• Psychological/Psychiatric evaluation (access to mental health evaluation and services)	

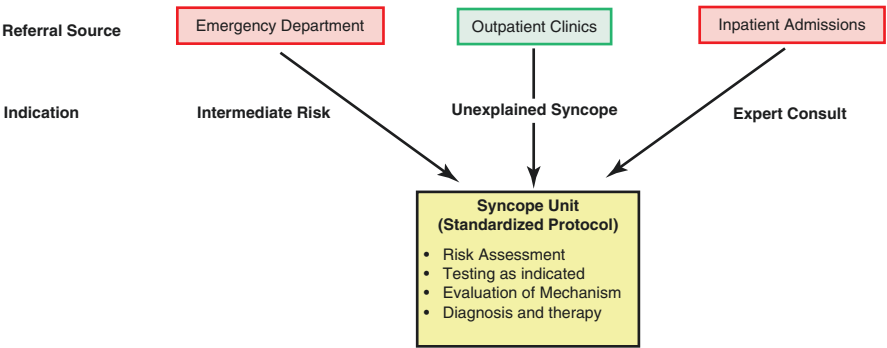


Fig. 17.2 Sources of referral to a syncope unit (SU) including indications

The presence of a syncope specialist is essential for any SU. A syncope specialist is a practitioner who has comprehensive knowledge of the historical cues and physical findings of the various forms of T-LOC. The use of standardized algorithms will ensure a clear diagnostic and therapeutic pathway and decrease variability among the syncope specialists. The tests and assessments that should be available in the SU are detailed in Table 17.2. Referrals to SUs include patients from the ED, outpatient clinics, and inpatient admissions that require an evaluation from a syncope expert (Fig. 17.2).

17.4 Syncope Units Models

Syncope evaluation units vary in design and include both physical and virtual unit models. These models have been shown to reduce overall healthcare service use and increase rate of diagnosis [9]. The United Kingdom (UK) has an increasing number

of SUs, which are listed by STARS (Syncope Trust and Anoxic Reflex Seizures), a charitable organization providing information to patients about syncope and related conditions, <http://www.heartrhythmalliance.org/stars/uk/>. Italy has an expanding number of SUs, which are listed by GIMSI (Gruppo Italiano Multidisciplinare per lo studio della Sincope), <http://www.gimsi.it/>. These information sites include available SUs that are geographically close for inquiring patients. Several countries including Ireland, USA, Canada, Spain, Portugal, France, Netherlands, Sweden, Japan, Brazil, Romania, Poland, and Slovakia are developing similar syncope evaluation units. Below are some examples of physical and virtual SUs.

Physical Unit: The Day-Care Syncope Evaluation Unit was established in Newcastle, United Kingdom and is referred to as the Newcastle Rapid Access Falls and Syncope Service (FASS). It is located in an outpatient facility area within a general hospital. Patients are referred from community clinics, the emergency department, and medical inpatient services. A multidisciplinary approach is utilized based on national and international evidence-based diagnostic algorithms for older patients with falls and all adult age groups with T-LOC. The unit is managed by an internist/geriatrician with support from specialty trained nurses. Consultation with cardiology and neurology services is also available. Defined protocols and educational methods are an integral function of the Falls and Syncope Services for older people [10]. The Rapid Access Blackouts Triage Clinic (RABCT) is another service provided in the UK for patients presenting with blackouts. It is designed to provide rapid clinical assessment in the outpatient setting with rapid referral to a specialist where appropriate [11].

The Faint and Fall Clinic was established in the USA as a resource for ED physicians and providers who see patients with syncope/collapse. It uses a multidisciplinary approach to evaluating patients with fainting spells or falls. The clinic is managed by a cardiologist and geriatrician and supported by trained advanced nurse practitioners. Providers in the clinic use a web-based decision-making interactive software that integrates up-to-date guidelines for risk assessment and management of patients with T-LOC. An evaluation by a Neurologist is also available when indicated [12].

The Syncope Observational Unit in the emergency department is an example of an outpatient unit managed by an experienced emergency physician with support from specialty trained nurses and medical specialists (e.g., electrophysiologists, neurologists). Intermediate-risk patients presenting to the ED with syncope are admitted to the unit for monitoring and guideline-based evaluation. This type of unit was utilized in both the SEEDS (United States) and EDOSP (Spain) studies demonstrating improved diagnostic yield and reduced hospital admission and total length of hospital stay for intermediate-risk patients [13].

Virtual SU: Utilizing recent guideline-based flowcharts and software, a functional SU is a virtual unit supervised by a cardiologist and supported by personnel trained in syncope/collapse evaluation. It was first introduced in Italy and later adopted in other countries. Patients are referred to the unit as outpatients or from the ED. Access to a specialist (e.g., in person, by telephone) is essential for appropriate function of

the unit. Studies using this model reported similar outcomes to physical SUs including decreased hospital admissions and overall cost, and improvement in diagnostic yield [14].

17.5 Follow-up and Outcome

Regardless of the SU model used, once the work-up is complete and a therapy is initiated, the patient should receive a concise report along with specific instructions. A written comprehensive report including follow-up plan should also be sent to the referring provider. The follow-up can be in person, via telephone, or using a secure electronic medical record (EMR) messaging. Appropriate follow-up is important to assess the efficacy of treatment, establish a diagnosis in patients with unexplained syncope who are undergoing prolonged ECG monitoring, and re-evaluation in case of syncope recurrence.

With the adoption of a standardized approach, health care systems are likely to see a decrease in the rate of hospitalizations, an increase in the rate of diagnosis and diminished costs per patient. However, dissemination of this approach has proven to be a challenge for many reasons including the wide spectrum of providers who see patients with syncope, and the required buy-in from various stakeholders. Reassuring all parties that these changes are in the best interest of patients is key to begin the discussion and ultimately the implementation of a SU.

17.6 Future Perspectives

The specific goals in evaluating a patient with syncope include identifying prognostic risk (death, severe adverse events, and syncope recurrence), and ascertaining the specific cause of the LOC in order to apply the appropriate treatment strategy. While risk assessment is done at initial evaluation, determining the mechanism can be a challenge since the events are often transient in nature. One of the major roles of SUs is establishing longitudinal follow-up to ensure the proper diagnosis is made, thus avoiding future repetition of tests in cases of syncope recurrence. Standardized protocols including prolonged cardiac monitoring provide an opportunity to determine the mechanism instead of assuming causality based on abnormal test findings such as with invasive electrophysiologic studies and tilt table testing.

There is an ongoing debate whether SUs are superior in efficiency and outcome to a syncope specialist. This is a valid concern given the significant cost of establishing a SU, particularly a physical one. While there is a need for additional studies in this area, most providers also recognize that the availability of syncope specialists continues to be a problem at a regional, national, and international level. Therefore, the authors propose a new approach that involves equipping providers on the front line with a web-based online interactive decision-making tool that allows better

adherence to established syncope guidelines. Access to such a tool could provide educational material and suggestions to non-syncope experts regarding the most appropriate up-to-date evidence-based therapy. Studies using interactive decision-making software coupled with a standardized syncope assessment reported increased adherence to guidelines resulting in decreased admission rate, decline in unnecessary testing, improvement in diagnostic yield, and reduction in overall cost per diagnosis [8]. We recently compared the clinical outcome of a SU run solely by a nurse practitioner assisted by an online faint-decision software and consultancy of a faint specialist through video conferencing, with a SU run by a syncope specialist [15]. We found a similar rate of diagnosis and even lesser cost per diagnosis with the nurse practitioner outreach model. This model allows the dissemination of standardized high-quality syncope care in areas where immediate access to a syncope specialist is not available.

Lastly, it is important to note that significant overlap exists between syncope and falls in the older population [16]. Advanced age is associated with increased susceptibility to syncope due to impairments of heart rate and blood pressure regulation along with increased incidence of cardiac arrhythmias. Because of amnesia and frequent absence of witnesses, older patients with recurrent T-LOC often present with falls. Furthermore, transient drop in blood pressure might result in loss of postural tone and a fall without any true LOC. Therefore, consideration should be given for the integration of falls in SUs in order to provide comprehensive geriatric assessment including cardiovascular evaluation.

17.7 Summary

Syncope units have been developed with the intent of ensuring a systematic approach toward the evaluation of patients with transient loss of consciousness from risk stratification to diagnosis, therapy, and follow-up. The success of any SU requires a physician-champion and a buy-in from all stakeholders. The results are beneficial to not only patients but also health payers and health care systems. These units can also have a major role in education and create an opportunity for innovation in health care delivery.

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Part IV
Selected Testing: When and How

Chapter 18

Role of Head and Cardiac Imaging, and Cardiac Stress Testing for Syncope



Mohammed Ruzieh and Blair P. Grubb

18.1 Introduction

There are multiple causes of syncope and some are potentially fatal. Nonetheless, vasovagal syncope remains the most common cause of syncope, and although it is associated with high recurrence rate, it has a benign course [1]. The cause of syncope can be revealed by history and physical examination in the majority of patients. Despite that, many patients undergo unnecessarily extensive investigations that have high cost but low diagnostic utility. In this chapter, we discuss the role of head imaging, as well as cardiac imaging and cardiac stress testing in patients with syncope.

18.2 Role of Head Imaging

Syncope secondary to structural brain abnormalities or carotid artery disease is rare. Nonetheless, brain MRI and CT, and CUS are frequently ordered in patients with uncomplicated syncope. In a systematic review of 15 investigational syncope studies [2], MRI was ordered in 432 of 4103 patients (10.5%), CT scan was ordered in 2434 of 4250 patients (57.3%), and CUS was ordered in 751 of 4220 patients (17.8%). Even though abnormal test results were reported in a high proportion of patients; MRI (19.2%), CT (11.6%), and CUS (21.3%), most abnormalities were thought not to be relevant to syncope, and almost all studies, except for one (0.02%) CT scan, did not provide new informative results. In other words, for every 10,000

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Table 18.1 Recommendations on head imaging in patients with syncope

Recommendation	ESC 2018		ACC/AHA 2017	
	Class	Level of evidence	Class	Level of evidence
Routine brain MRI	III	B	III	B
Routine brain CT	III	B	III	B
Routine CUS	III	B	III	B
Brain MRI if parkinsonism, ataxia, or cognitive impairment is suspected	I	C	No comment	

ACC American College of Cardiology, *AHA* American Heart Association, *ESC* European Society of Cardiology

brain MRI, CT, or CUS that are performed, only two might lead to change in management.

Given high cost, radiation risk (with CT scan), and very low test utility, both the American and European guidelines [3, 4] recommend against the routine use of head imaging in evaluating patients with syncope, (Table 18.1). Nonetheless, brain imaging with MRI or CT is reasonable when syncope results in significant head trauma or when there is high suspicion for parkinsonism, ataxia, or cognitive impairment.

18.3 Role of Cardiac Imaging

Syncope due to underlying structural heart disease is not infrequent and is associated with worse prognosis [5]. Therefore, cardiac imaging using echocardiography is useful after careful history, physical examination, and an electrocardiogram (ECG) in selected patients where a structural heart disease is suspected to be the cause of syncope. In a study of 650 patients with unexplained syncope, routine echocardiography was not relevant in patients with negative cardiac history and a normal ECG. Nonetheless, it identified severe aortic stenosis in 8 out of 20 patients who were suspected to have it [6].

Table 18.2 lists potential cardiac causes of syncope, with the supportive history, physical examination, and ECG findings. The most recent European and American guidelines give echocardiography class I and class IIa recommendation, respectively, in evaluating syncope patients with suspected structural heart disease, Table 18.3. Cardiac imaging using MRI offers higher spatial resolution compared to echocardiography and is useful in selected cases when the initial evaluation by echocardiogram is inconclusive such as in suspected cases of arrhythmogenic right ventricular cardiomyopathy (ARVC) or hypertrophic cardiomyopathy. Finally, evaluation for ischemic heart disease using stress echocardiography, nuclear perfusion scan, or coronary angiogram should not be part of the syncope evaluation unless cardiac ischemia is suspected based on the history, similar to patients without syncope.

Table 18.2 Common cardiac causes of syncope where cardiac imaging can be helpful

Condition	Supportive history	Supportive physical examinations findings	Supportive electrocardiogram
Severe aortic stenosis	Exertional syncope. Maybe associated with angina or heart failure	Loud late peaking systolic murmur. Prominent S4. Pulsus parvus et tardus	Criteria for left ventricular hypertrophy
Hypertrophic obstructive cardiomyopathy	Exertional syncope. Palpitations. Angina. Heart failure. Positive family history	Double apical impulse. Double carotid pulse. Systolic ejection crescendo-decrescendo murmur that increases with any decrease in preload	Criteria for left ventricular hypertrophy. Prominent Q waves in the anterior and lateral leads. ST-T wave abnormalities
Arrhythmogenic right ventricular cardiomyopathy	Exertional syncope. Palpitations. Heart failure. Positive family history	Signs of right ventricular failure in late stages (elevated jugular venous pressure, liver congestion, lower extremity edema)	T-wave inversion in the right precordial leads. Epsilon wave. Ventricular arrhythmias with a left bundle-branch block pattern. Inverted T waves in the inferolateral leads and/or ventricular arrhythmias with a right bundle-branch block (in left-sided disease)
Pericardial tamponade	Syncope with rest or exertion. Chest tightness. Shortness of breath. Recent pericarditis. History of malignant disease. Renal failure. Recent cardiac interventions or devices. Thyroid disease	Distant heart sounds. Elevated jugular venous pressure. Other physical examinations are dependent on the cause	Low voltage. Electrical alternans
Aortic dissection	Syncope with rest or exertion. Sudden onset chest pain with radiation to intrascapular area. Onset of symptoms maybe associated with neurological symptoms or symptoms of limb ischemia	More than 20 mm Hg difference in blood pressure between arms. Wide pulse pressure (if dissection results in aortic regurgitation). Signs of cardiac tamponade. Neurological deficits. Signs of peripheral ischemia	Findings of acute coronary syndrome if dissection extends to involve the coronary arteries (the right coronary artery is the most commonly involved)
Obstructive cardiac tumors	Syncope with rest or exertion. Shortness of breath. Weight loss. Fever. Night sweats. Malignant cancers outside the heart. Neurological symptoms (if tumor results in systemic embolization)	A diastolic atrial rumble (if tumor is obstructing the mitral or tricuspid annulus). Myxomas of other organs. Neurological deficits (if embolization occurs)	Variable dependent on tumor location and invasion or nearby structure, which can result in myocardial ischemia or pericardial effusion

Table 18.3 Recommendations on cardiac imaging in patients with syncope

Recommendation	ESC 2018		ACC/AHA 2017	
	Class	Level of evidence	Class	Level of evidence
Echocardiogram when structural heart disease is suspected	I	B	Ila	B
Cardiac MRI	Can be considered		Ilb	B

ACC American College of Cardiology, AHA American Heart association, ESC European Society of Cardiology

18.4 Role of Cardiac Stress Testing

Exercise-related syncope can be further subdivided into syncope during exercise and syncope after exercise. While the former is likely due to cardiac causes, the latter is often related to exaggerated vasovagal response. In patients with exercise-induced syncope, exercise treadmill testing under ECG monitoring can identify tachyarrhythmias in conditions such as ARVC, type I long QT syndrome, hypertrophic cardiomyopathy, and catecholaminergic polymorphic ventricular tachycardia (CPVT). Additionally, exercise induced high grade atrioventricular (AV) block can result from tachycardia even in patients with normal baseline ECG [7] or from exercise induced coronary ischemia or coronary spasm [8].

In selected cases, treadmill exercise echocardiography is required when exercise induced left ventricular outflow tract (LVOT) obstruction or exercise induced pulmonary hypertension is suspected.

The most recent European and American guidelines give exercise testing a class I and class Ila recommendation, respectively, in patients who experience syncope during exercise.

18.5 Conclusion

Detailed history and thorough physical examinations will identify the cause of syncope in the majority of patients. Head imaging should not be routinely done and is only recommended when a neurological cause of syncope/collapse is suspected. Similarly, cardiac imaging and cardiac stress testing are only appropriate when syncope/collapse is thought to be due to a structural heart disease or an arrhythmia.

Conflict of Interest None

Disclosure None

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Chapter 19

The Autonomic Laboratory for Evaluating Syncope/Collapse: Investigations and Their Implications



Christopher J. Mathias, Andrew P. Owens, and Valeria Iodice

19.1 Introduction

Syncope and collapse occur across the age spectrum with an increased prevalence in certain age groups. In the Framingham study with subjects over the age of 20, 3% of men and 3.5% of women experienced syncope/collapse on at least one occasion, with a marked increase in older subjects [1]. In teenagers and adolescents the prevalence is also high [2]. Syncope and collapse often blur with commonly used names such as ‘funny turns’, ‘faints’, ‘falls’, and it is likely that the incidence is even higher than reported. Such episodes may be the result of neurological (autonomic and non-autonomic), cardiac, and metabolic, dysfunction [3].

Falls and syncope account for 3% emergency room visits and 6% of all hospital admissions, affecting 6/1000 people each year [4]. United Kingdom (UK) ambulance services respond to between 300,000 and 400,000 emergency calls for falls

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and syncopal episodes in older people annually [5], with up to 50% of patients seen being taken to hospital. These patients remain at risk of recurrent episodes in the subsequent 12 months, with a 30% incidence of sustaining a fracture or dislocation due to faints or falls. The prevalence, incidence, and recurrence of syncope/collapse increase with age [6]. Once admitted, patient assessment can fall between a number of departments that include Accident and Emergency Medicine, Cardiology, General Medicine, Geriatric Medicine, and Neurology.

This chapter will focus on the autonomic laboratory and its role in investigating autonomic nervous system causes of syncope and collapse, including:

- diagnosing an autonomic condition or excluding an autonomic aetiology.
- ascertaining the underlying pathophysiological factors of relevance and allied disease processes.
- determining additional and associated factors that will aid management.

19.1.1 Clinical Evaluation

Clinical evaluation is of particular importance, especially in guidance of which autonomic tests should be performed. A detailed history should cover the period before, during, and after the episode(s). Information from witnesses who may be partners, family, carers, or passers-by can be of value. With recurrent episodes a reliable account may be difficult, especially with blurring of details over time. The history should comprehensively probe features of allied disorders and conditions which may contribute to syncope and collapse. These include medication and also recreational drug use where relevant, activities of daily living that cause vasodilatation (such as eating, bathing, exercise), and factors resulting in carotid baroreceptor stimulation (such as shaving, head turning).

The most common causes of pre-syncope and syncope are intermittent episodes of autonomic dysfunction, that include autonomic (previously also known as neurally) mediated syncope (AMS), and a proportion who have the postural tachycardia syndrome (PoTS) (Table 19.1). These usually occur while upright.

AMS broadly may be considered under:

- Vasovagal syncope (VVS), the most common, accounting for the majority [7] and predominantly in females <40 years. In VVS, cardiac parasympathetic and blood vessels/cardiac sympathetic innervation are transiently involved (Fig 19.1a, b, and c).
- Carotid sinus syndrome typically in those >50 years, resulting from enhanced afferent carotid baroreceptor activity/hypersensitivity [9].
- Situational syncope attributable to a specific stimulus, often raising intrathoracic pressure (e.g., cough syncope, defecation syncope, trumpet blowers syncope, etc.).

There may be a strong family history in VVS [9, 10]. In some, provoking factors such as blood-injection-injury phobia can precipitate an episode [11] which may

Table 19.1 Outline classification of autonomic disorders

Intermittent Autonomic Dysfunction
<i>Autonomic (Neurally) Mediated Syncope</i>
Vasovagal syncope
Carotid sinus hypersensitivity
Situational syncope
<i>Postural tachycardia syndrome</i>
Resulting From Autonomic Damage and Failure
<i>Primary</i>
<i>Acute/subacute dysautonomias</i>
Pure pan-dysautonomia
Pan-dysautonomia with neurological features
Pure cholinergic dysautonomia
<i>Chronic autonomic failure syndromes</i>
Pure autonomic failure
Multiple system atrophy (MSA, Shy–Drager syndrome)
Parkinson’s disease with autonomic failure
Lewy body disease
<i>Secondary</i>
<i>Congenital</i>
Nerve growth factor deficiency
<i>Hereditary</i>
<i>Autosomal dominant trait</i>
Familial amyloid neuropathy
<i>Autosomal recessive trait</i>
Familial dysautonomia—Riley–Day syndrome
Dopamine β -hydroxylase deficiency
<i>Metabolic diseases</i>
Diabetes mellitus
Chronic renal failure
Chronic liver disease
Alcohol-induced
<i>Inflammatory</i>
Guillain–Barré syndrome
Transverse myelitis
<i>Infections</i>
Bacterial (tetanus) Viral (HIV infection)
<i>Neoplasia</i>
Brain tumours—especially of third ventricle or posterior fossa
Paraneoplastic, especially adenocarcinoma of lung and pancreas
<i>Surgery</i>
Vagotomy and drainage procedures—‘dumping syndrome’
<i>Trauma</i>
Cervical and high thoracic spinal cord transection
<i>Drugs, chemicals, toxins</i>
By direct effects or by causing a neuropathy

begin when they are teenagers. In others associations and conditioning, may contribute to VVS and/or pseudosyncope/functional non-syncopal collapse [12]. In subjects over 50, carotid sinus hypersensitivity leading to carotid sinus syndrome may be associated with triggers, such as head turning or shaving. In situational syncope, induction of a Valsalva manoeuvre may be causative, as in weightlifters and woodwind musicians, or during coughing or micturition.

In PoTS, palpitations and dizziness occur usually while upright and are relieved by lying flat (Fig. 19.2). A proportion (in our experience around 30%) faint especially initially, with palpitations and other pre-syncopal features enabling them to take preventative action. Factors in daily life causing vasodilatation, such as food ingestion, exertion, and heat often worsen symptoms. PoTS is more common in

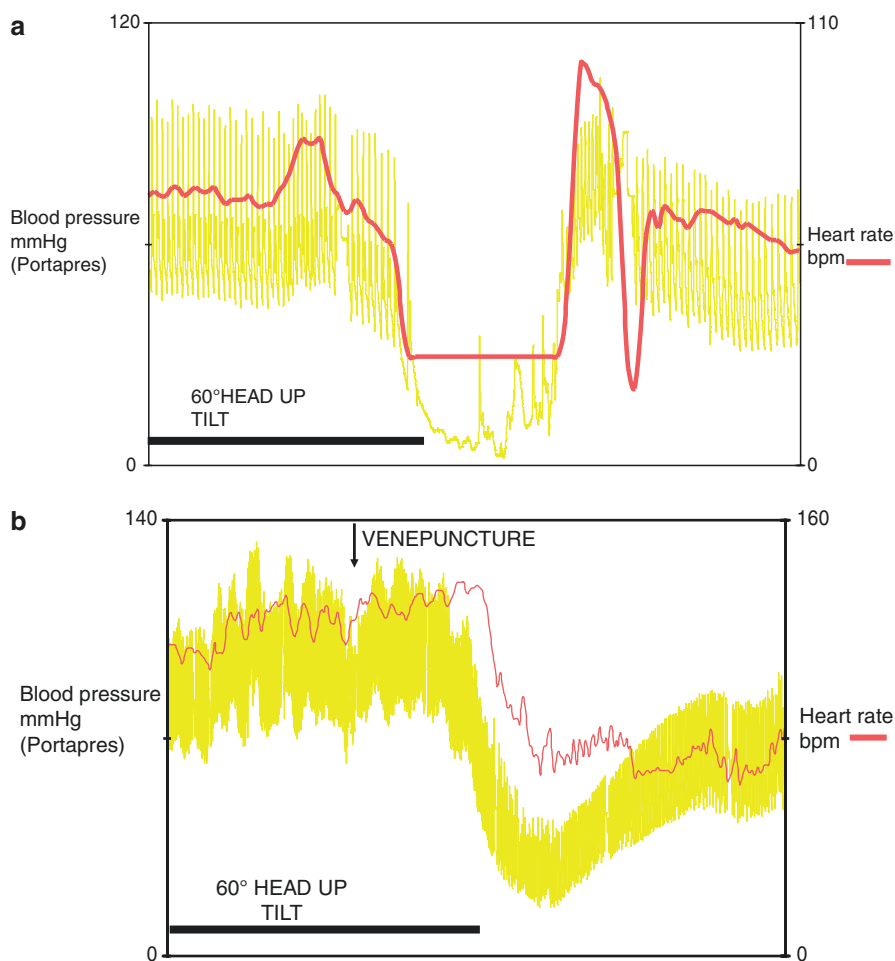


Fig. 19.1 Blood pressure (BP) and heart rate (HR) during head-up tilt in autonomic mediated syncope. In the vasodepressor form (a), sympathetic withdrawal lowers BP. In the cardioinhibitory form (b) increased parasympathetic activity precipitates a pronounced HR fall. In the most common mixed form (c) both BP and HR fall. From Mathias et al. [8]

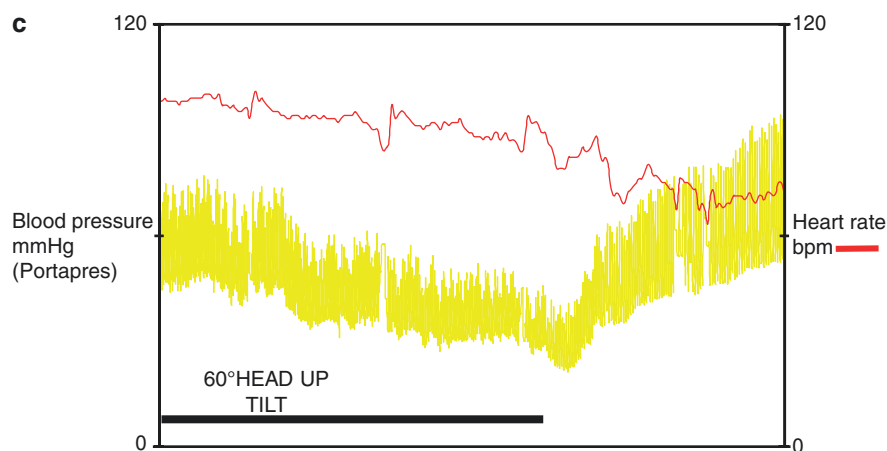


Fig. 19.1 (continued)

young females and may be associated with the joint hypermobile form of Ehlers–Danlos syndrome (E-DS) [13]. Lack of collagen and connective tissue around blood vessels may contribute to peripheral vascular pooling, especially in the lower limbs while upright, and can be observed when upright, such as during head-up tilt.

Syncope and collapse in older subjects are more likely to result from primary autonomic disorders or complicate diseases that cause autonomic damage and failure (Table 19.1). Some of these conditions are irreversible and often progressive if resultant from neurodegeneration, such as in Parkinson’s disease and multiple system atrophy (MSA). They include conditions such as acute and subacute dysautonomia (in some with an autoimmune basis increasingly recognised with antibody testing), or pure autonomic failure (PAF, with no known aetiology). Syncope may occur in typical and also atypical Parkinsonian diseases, the latter including MSA and diffuse Lewy body disease. It may result from hereditary disorders such as transthyretin amyloidosis, or common metabolic diseases such as Type 1 and Type 2 diabetes mellitus. Syncope may occur after trauma (high thoracic and cervical spinal cord transection), after surgery (dumping syndrome post-vagotomy), and with neoplasia (paraneoplastic). The history thus should consider various associated aspects of relevance, despite primarily concentrating on syncope and collapse.

The clinical examination should be comprehensive, with a focus on the cardiovascular system. Blood pressure (BP) and heart rate (HR) should be measured while supine and after standing, ideally using beat-to-beat recordings for at least 3 min. Orthostatic hypotension often is a pointer towards autonomic failure. Medication, especially with vasodilatory effects may be contributory, and a detailed drug history is essential. Even when an autonomic aetiology is the main reason for referral other causes, especially cardiac, need to be excluded.

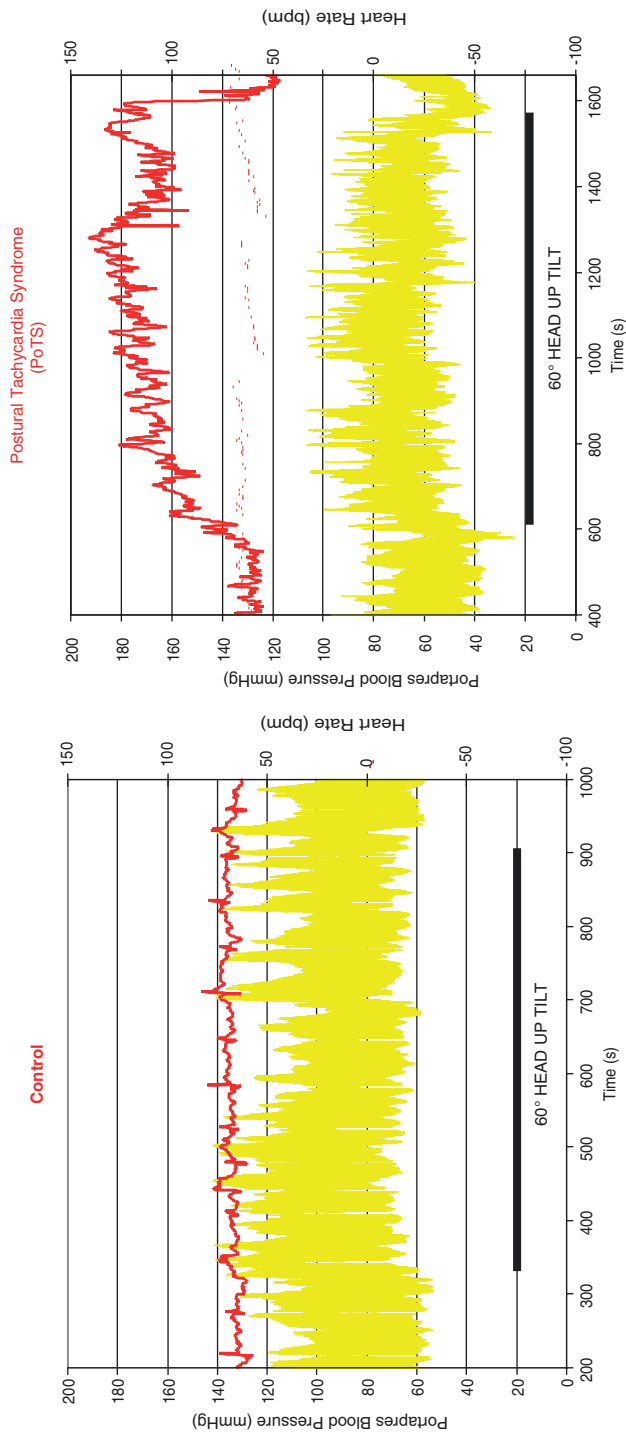


Fig. 19.2 BP and HR responses in a normal subject (left panel), and in the postural tachycardia syndrome (PoTS) (right panel). In the latter HR rises excessively without a fall in BP. From Mathias et al. [13]

19.1.2 Autonomic Investigations

The key aims in the autonomic testing laboratory [8] are to determine:

- If cardiovascular autonomic function (affecting the sympathetic and/or parasympathetic nervous system) is normal or abnormal?
- If normal, whether additional tests are needed to unmask an abnormality? This is of particular importance in intermittent autonomic dysfunction.
- If abnormal, which tests are needed to confirm the degree and type of autonomic impairment to aid diagnosis and management?

The key tests are outlined in Table 19.2. The initial autonomic screening tests will determine if sympathetic and parasympathetic pathways to blood vessels and the heart are affected, as occurs with autonomic failure. They include the responses to standing and to head-up tilt. In autonomic failure, postural hypotension occurs usually within 10 min of tilt. In the intermittent disorders, prolonged head-up tilt may be needed, ideally continued for 45 min and should include observations for peripheral vascular pooling, especially in the lower limbs as often occurs in PoTS. We do not use pharmacological agents such as GTN, as these are not relevant to daily life. Furthermore in some prone to vascular pooling as a result of concomitant medication or their condition (such as PoTS), GTN may be anxiogenic (complicating differentiation of psychogenic from orthostatic tachycardia), and cause considerable concern.

The major activities of daily living that contribute further to vasodilatation while upright are food ingestion and exertion. Testing the response to these can provide valuable information to guide patients and moreover determine whether additional strategies or medication is needed. There are accepted protocols for these [8].

Table 19.2 Outline of cardiovascular autonomic investigations in syncope/collapse

Physiological	Head-up tilt (60°) ^a ; Standing ^a
	Pressor stimuli (for sympathetic function)—isometric exercise ^a , cutaneous cold ^a , mental arithmetic ^a
	Heart rate responses (for parasympathetic function)—deep breathing ^a , hyperventilation ^a , Valsalva manoeuvre ^a
	Liquid meal challenge—BP and HR responses to head-up tilt before and after ingestion
	Supine exercise—BP and HR responses to standing before and after exercise
	Head and neck movements. Carotid sinus massage
	Arm movements, especially above head, supine, and tilted
	24-h ambulatory BP and HR autonomic profile using the autonomic protocol
Biochemical	Plasma noradrenaline, adrenaline, dopamine—supine and head-up tilt or standing Urinary catecholamines. Plasma renin activity and aldosterone

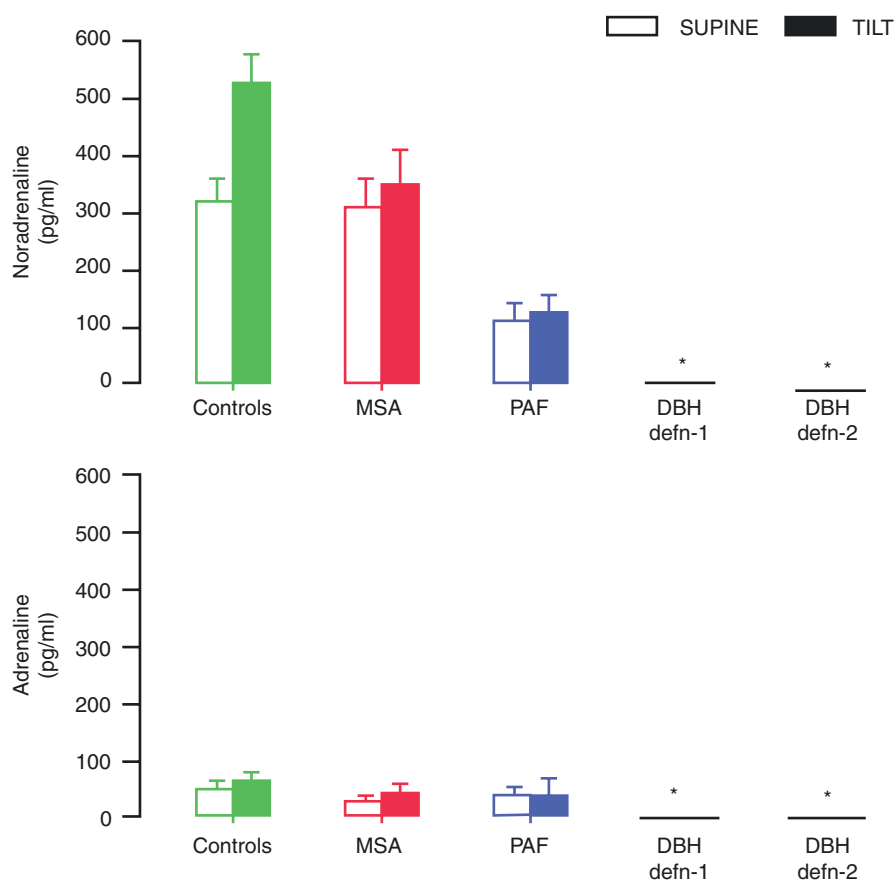
^aindicate autonomic screening tests used in our London Units

A balanced liquid test meal will determine if there is post-prandial exacerbation of BP lowering, HR elevation, and symptom provocation. Supine graded exercise separates the effects of gravity from exertion; standing after supine exercise when increased blood flow is not compensated by the calf muscle pump can unmask exercise-induced hypotension in autonomic failure and cause excessive tachycardia in PoTS.

In those with blood-injection-injury phobia, psychogenic stimuli may inadvertently induce an episode of syncope, such as when blood is taken for the measurement of plasma catecholamine levels. Plasma noradrenaline, adrenaline, and dopamine levels can determine whether autonomic failure is central or peripheral. In central and pre-ganglionic lesions such as in MSA, plasma noradrenaline is normal while supine with an impaired rise when upright. In peripheral and post-ganglionic lesions such as in PAF, supine plasma noradrenaline is low with minimal change or no rise when upright. Plasma dopamine levels in these conditions usually are normal. In rare cases such as dopamine beta hydroxylase deficiency, basal noradrenaline and adrenaline levels are extremely low with elevated plasma dopamine confirming the enzymatic deficit (Fig. 19.3) [14].

Orthostatic hypotension often is a pointer towards autonomic damage and failure. The fall in blood pressure when upright usually recovers immediately on return to the horizontal position (Fig. 19.4). In some there may be a blood pressure overshoot resulting in supine hypertension. Food and exercise often enhance orthostatic hypotension, because of additional vasodilatation in the splanchnic region and in exercising muscle. Drugs with even mild hypotensive effects can unmask or worsen orthostatic hypotension when there is autonomic impairment.

In addition to laboratory testing, home 24-h ambulatory BP and HR recordings with the patient's daily routines provide valuable information if a clearly defined autonomic protocol is adhered to (Fig. 19.5a, b, and c) [15]. This can be combined with 24-h continuous ECG/HR recordings of the effects of different postures, activities of daily living, and circadian rhythm on digital biomarkers by correlating the time-stamped cardiovascular data with diary entries. They also may be of value in functional non-syncopal collapse/pseudosyncope, when fainting in the laboratory is not accompanied by the typical changes in BP and HR that results in cerebral hypoperfusion and subsequent loss of consciousness.



Plasma Noradrenaline & Adrenaline

Fig. 19.3 Plasma noradrenaline and adrenaline levels while supine and during head-up tilt in normal subjects and in the different forms of autonomic failure. Plasma noradrenaline does not rise in either MSA or PAF when upright. In each of the three groups plasma dopamine levels (not shown) are normal unlike a brother and sister with dopamine beta hydroxylase deficiency, with undetectable plasma noradrenaline and adrenaline but elevated levels of the precursor, dopamine. From Mathias et al. [14]

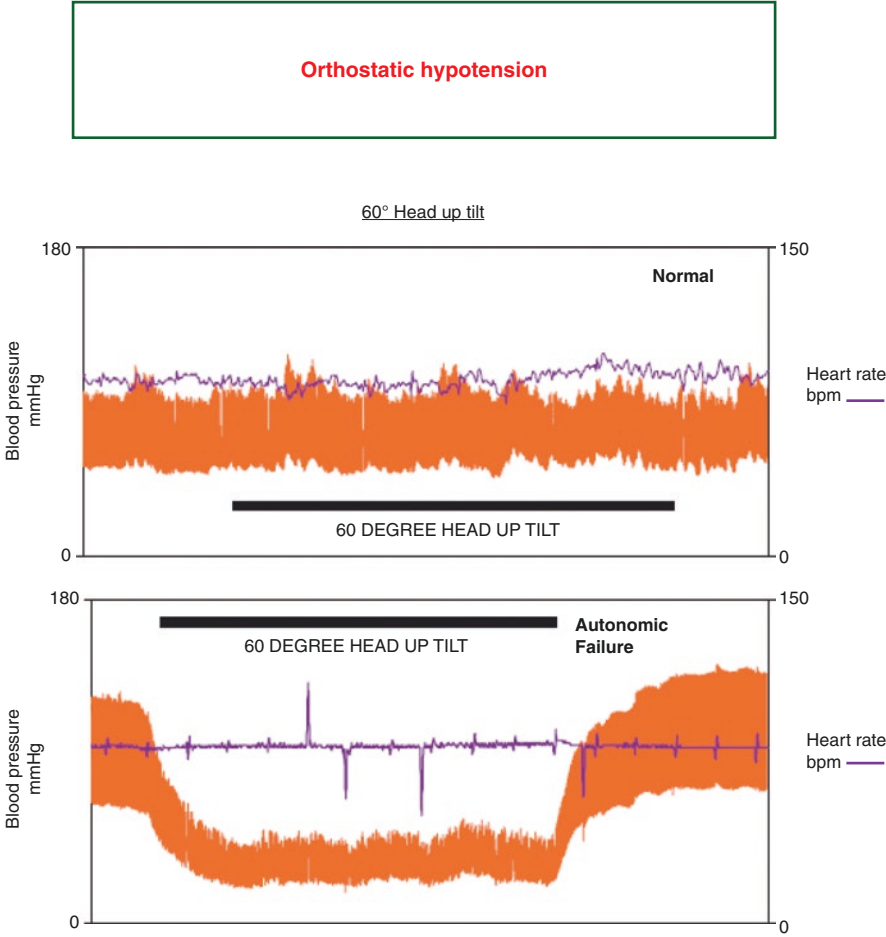


Fig. 19.4 BP and HR in a normal subject (upper panel) and in a patient with autonomic failure (lower panel). In the latter there is a marked fall in BP with minimal change in HR while upright, with BP recovery soon after return to the horizontal. From Mathias et al. [8]

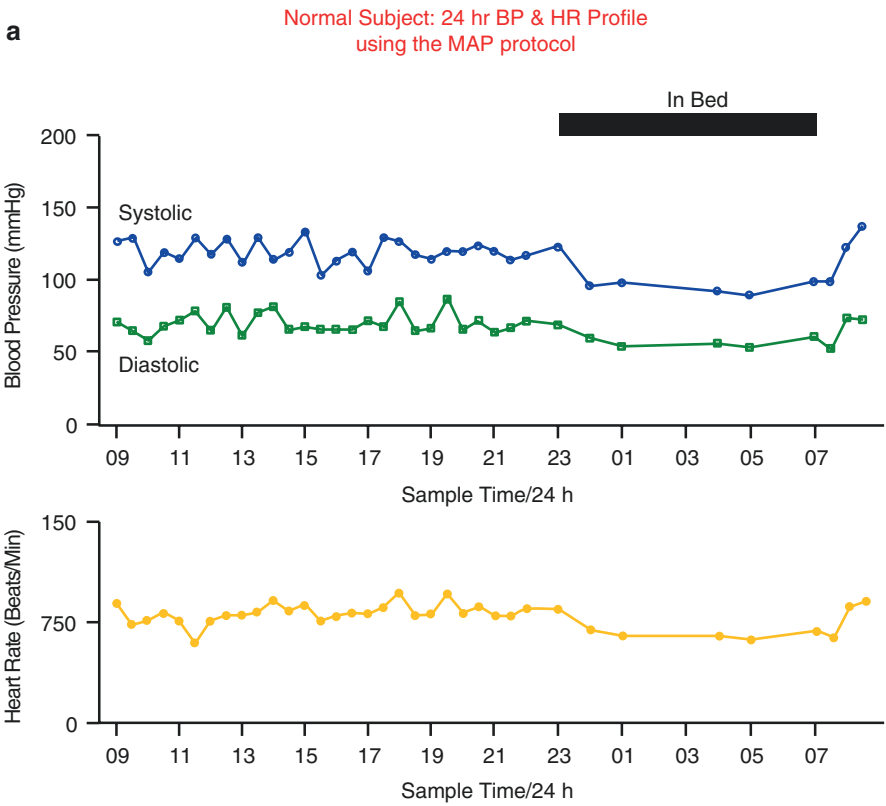


Fig. 19.5 24-h ambulatory BP and HR recordings using the Mathias et al autonomic protocol in a normal subject (**a**), and in subjects with autonomic failure (**b**), and PoTS (**c**)

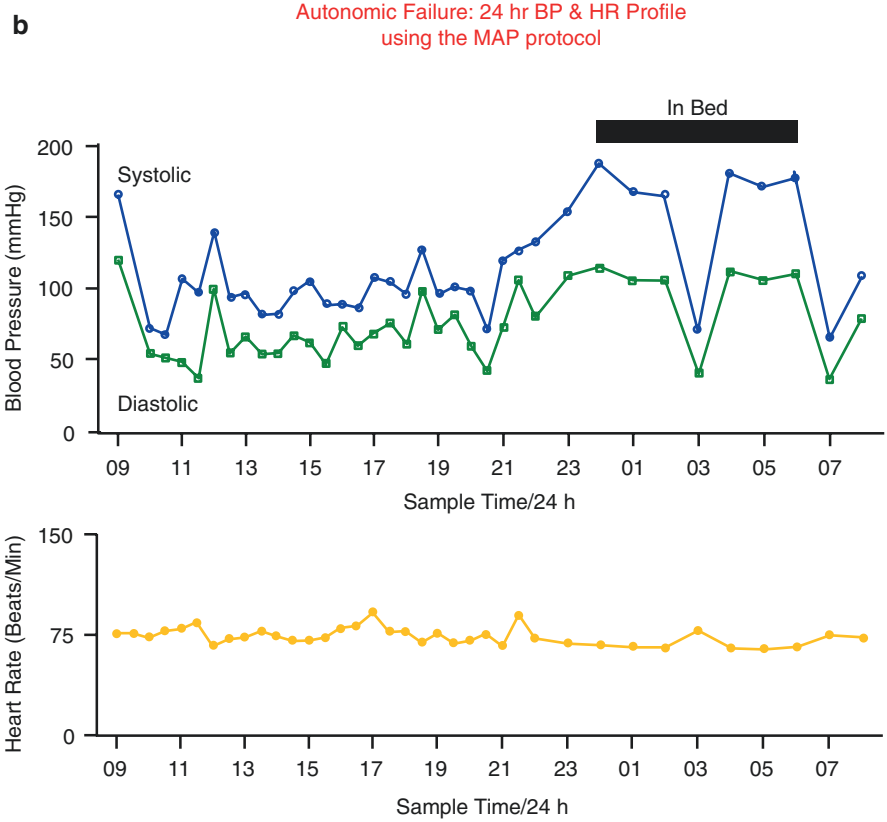


Fig. 19.5 (continued)

24 hour ambulatory BP & HR profile
using the MAP autonomic protocol

c

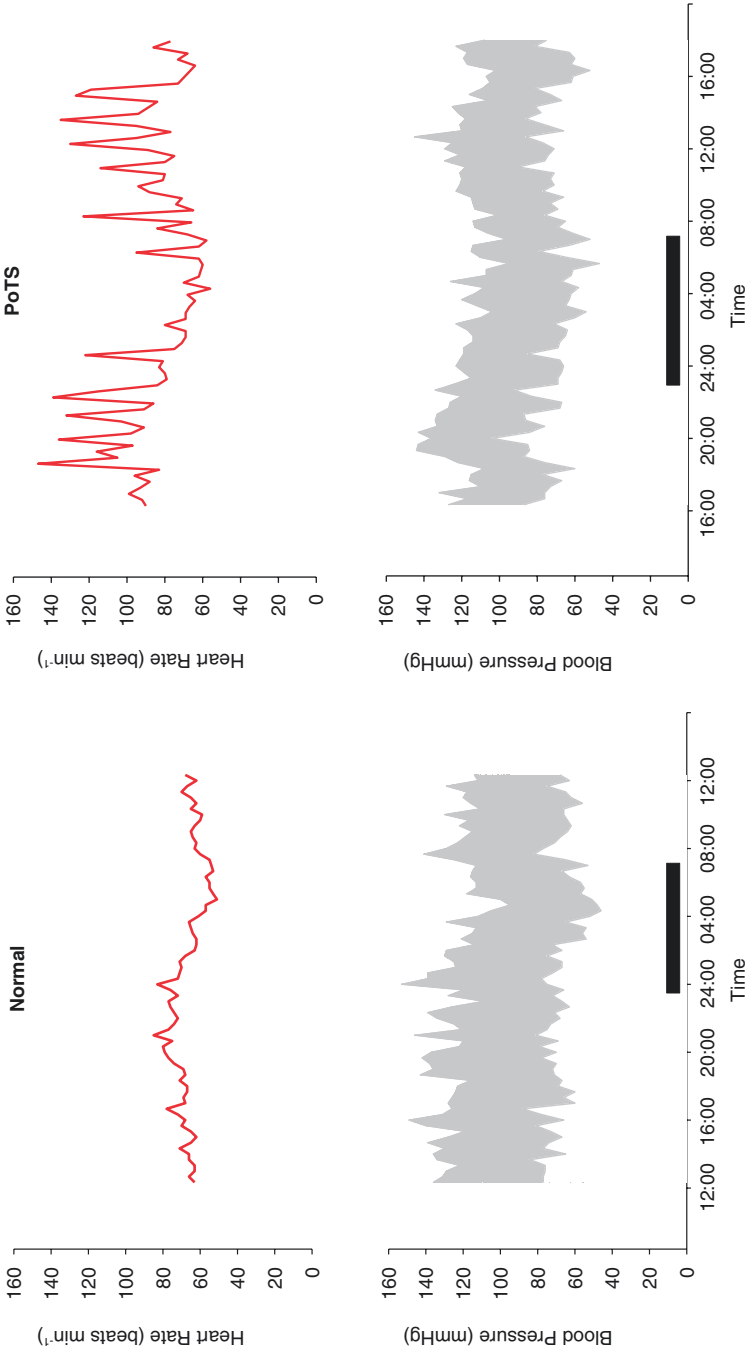


Fig. 19.5 (continued)

19.1.3 Conclusion

The autonomic laboratory ideally should provide safe and reproducible investigations that accurately enable diagnosis, understanding of underlying pathophysiological factors, and aid evidence-based management of syncope/collapse resulting from autonomic conditions. Exclusion of an underlying autonomic disorder or condition can itself be an important role. Although autonomic investigations are predominantly hospital laboratory-based, an important component is home ambulatory BP/HR recording using the autonomic protocol that includes a variety of events during activities of daily living. These 24-h BP/HR autonomic profiles additionally can track the benefits or otherwise of therapeutic interventions.

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Chapter 20

Utility of Video-EEG for Diagnosing and Understanding Transient Loss of Consciousness



Maryam Ghariq and Roland D. Thijs

Abbreviations

ECG	Electrocardiogram
EEG	Electroencephalogram
OH	Orthostatic hypotension
PPS	Psychogenic pseudosyncope
PNES	Psychogenic non-epileptic seizures
TLOC	Transient loss of consciousness
TTT	Tilt-table testing
VVS	Vasovagal syncope

20.1 Introduction

Transient loss of consciousness (TLOC) is a state of real or apparent loss of consciousness (LOC) characterised by amnesia for the period of unconsciousness, abnormal motor control and loss of responsiveness, with a short duration and spontaneous and complete recovery [1]. The two main diagnostic categories are ‘TLOC due to head trauma’ and ‘non-traumatic TLOC’. The latter group includes syncope, psychogenic pseudosyncope (with apparent LOC), psychogenic non-epileptic seizures, and some epileptic seizure types [1]. Psychogenic causes are included in the differential diagnosis of TLOC as the key features to establish LOC are often evaluated in retrospect and this assessment cannot reliably differentiate between real and apparent LOC.

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Diagnosing the cause of TLOC primarily relies on history taking, both from patients and eyewitnesses, but is often challenging and inaccurate due to overlapping symptoms, recall bias, and the lack of a reliable clinical algorithm to differentiate among all causes of TLOC [2]. A definite diagnosis may therefore require a recording of a typical event. The fast-rising digitisation and widespread use of smartphones have greatly improved the clinical work-up as spontaneous events are increasingly able to be recorded. It is, however, challenging for doctors to recognise the key semiological events of each form of TLOC even when presented with video evidence. Notably video tracings of psychogenic TLOC are easily misdiagnosed as epilepsy or syncope [3]. Conventional laboratory-based methods to record TLOC, including tilt-table testing (TTT) have also changed over the past years by the addition of both video and EEG recordings, yielding important insights into the key pathophysiological events.

In this chapter we aim to discuss key signs in syncope and their relation to EEG patterns and to highlight the semiological contrasts among the various types of syncope and the contrasts between syncope and the other forms of TLOC.

20.2 Syncope

TLOC in syncope results from global cerebral hypoperfusion which, in turn, is caused most often by a temporary low blood pressure (BP). Acute hypoxia such as during aircraft decompression at high altitude is a rare occurrence and could also contribute to syncope.

The decrease in BP may provoke a range of symptoms and signs dependent on the severity and the speed of the BP drop and the ability of the cerebral autoregulation to compensate for the low BP [4]. The prodromal signs and symptoms of syncope can be categorised into two groups. The first group comprises the consequences of the cerebral or retinal hypoperfusion due to the failure of the systemic perfusion. These symptoms and signs are similar for all causes of syncope. The second group is the complaints specific to the form of syncope and will be discussed in the next sections of this chapter.

Patients will only report symptoms of cerebral or retinal hypoperfusion if the fall in arterial pressure is slow enough to perceive symptoms and to store the sensations for recall later. Conversely, if the fall in arterial pressure is too steep, syncope may occur without prodromes. Certain subjects, most commonly the elderly, may even be unable to recall LOC ('amnesia for amnesia') and thus present with seemingly 'unexplained falls'. In essence, clinicians must be alert to the possibility that an 'unexplained fall' may in fact have been a syncope episode.

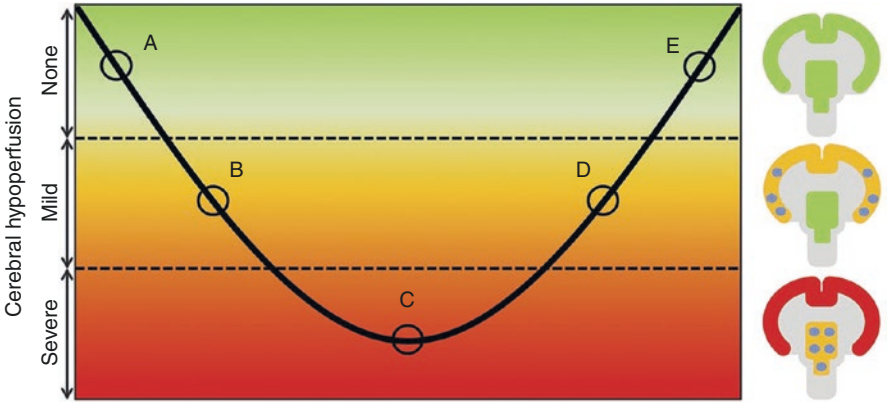
In true syncope, as BP decreases patients often report 'light-headedness' or dizziness as a first symptom of low cerebral perfusion. Other descriptions include 'emptiness in the head' or a 'swimming' sensation. If BP drop is slow, blurred vision and loss of peripheral vision may ensue as a second symptom relating to hypoperfusion of the retinae. Some subjects report 'grey out' (loss of colour vision) or 'black out' (darkened vision). Hearing loss (or diminished hearing volume) may occur

following loss of vision. With further decrease of the arterial pressure patients have difficulty concentrating and become unaware of their surroundings. A brief period of staring and an inability to move voluntarily may occur prior to complete syncope. Eventually when BP reaches the critical systolic pressure (~60 mmHg or lower) patients will lose postural tone and slump over or fall down and lose consciousness. LOC may also occur at higher BP when the BP drop is steep [5].

The clinical signs are linked to the severity of the cerebral hypoperfusion and reflected by the EEG patterns seen in syncope. Mild cerebral hypoperfusion will cause a ‘slow’ EEG pattern (a short-lasting period of abnormal delta waves), whereas in severe hypoperfusion a ‘slow-flat-slow’ pattern is seen: the slow pattern is followed by flattening of the EEG, in turn followed by a slow pattern of delta waves and then return to a normal EEG pattern. The EEG flattening is mostly seen in the setting of syncope involving asystole (e.g. cardioinhibitory vasovagal syncope), but can also occur in vasovagal syncope without asystole, other arrhythmias and in orthostatic hypotension [5].

The EEG only reflects the cortical brain functions. Signs during a flat EEG can thus not be explained by cortical functions and likely point towards brain stem activity (Table 20.1). Signs of brainstem dysfunction appear later than signs of cortical dysfunction, probably because the brainstem is more resistant to ischaemia. Some clinical signs are mostly seen during the slow phase of the EEG, some mostly during the flattening of EEG and some clinical features are present during both phases (Table 20.1).

Table 20.1 Schematic illustration of the relation between cerebral perfusion, cortical and brainstem functions and clinical signs in syncope



	A and E	B and D	C
Function			
– EEG	Normal	Slow	Flat
– Cortex	Normal	Reduced and disinhibition	Loss
– Brainstem	Normal	Normal	Reduced and disinhibition

(continued)

Table 20.1 (continued)

	A and E	B and D	C
Motor phenomena	None	Myoclonic jerks (<10)	Tonic postures (flexion > extension)
Other clinical signs	Inability to act	Loss of consciousness Dropping of head and jaw Head turning Eyes opening, dilated pupils, eyes upwards Oral automatisms Nystagmus	Roving eye movements, stertorous breathing, snoring

The graph shows a hypothetical time course of cerebral perfusion (bold line) and the corresponding EEG phases. Three situations are distinguished in the schematic graphs of the brain. (Green A & E) During normal cerebral perfusion: the EEG and function of the cortex and brainstem are normal, (Orange B & D) during mild hypoperfusion: the EEG has a slow pattern and some cortical functions are impaired while cortical disinhibition also occurs; brainstem functions normally; and jerks may be observed, (Red C) during severe hypoperfusion: the EEG has a slow-flat-slow pattern; cortical function is almost completely lost; disinhibition occurs in the brainstem; and tonic postures may be observed. The figures on the right represent the cortex and brainstem during the three phases. Colour legend: green = normal function; yellow = reduced function with EEG slowing; blue = disinhibition; red = loss of function with flattening of the EEG. Reproduced with permission from Neurology @ Wolters Kluwer Health

LOC usually starts in the slow phase. Eye opening and loss of muscle tone (e.g. head dropping) and a vacant expression often constitute the very first signs and are usually followed by a large number of other motor phenomena varying between subjects and between events. Myoclonic jerks are seen in about half of the cases and usually appear in syncope after the subject has fallen down [6]. The jerks are strongly associated with the slow phase of the EEG. If a second bout of myoclonic jerks occurs this starts during the second slow phase. The jerks rarely occur during the flat EEG, thus indicating that their presence signifies decreased but not complete shut-down of cortical activity. The number of jerks is rarely more than ten. The jerks are asynchronous and can be restricted to one side. The eyes are often closed before LOC, but open at onset of unconsciousness, with the pupils mostly directed upwards. If head turning is present, it starts quite early relative to the slow phase.

Oral automatisms are seen in about half of the syncope patients (during tilt-induced syncope) and may occur both during the slow phase of the EEG as well as during the flat phase. Snoring, gasping, roving eye movements, making sounds, and posturing are strongly associated with EEG flattening and thus probably reflect brainstem activity.

The duration of unconsciousness is never more than 1 minute. Eyewitnesses may, however, report longer durations due to the emotional impact of the situation [2]. Subjects rarely bite their tongue, if tongue biting occurs it concerns the tip of the tongue. Urine incontinence can occur during syncope, but faecal incontinence is rare.

In all forms of syncope patients recover quickly and are almost immediately clear-headed. Fatigue could occur for varying durations after vasovagal syncope. If any disorientation would occur, it likely lasts <10 s. The only exception to the rule might be those who are kept upright during the event and thus suffer from a more severe and prolonged period of brain anoxia [7]. The duration of syncope is usually too short to cause observable brain damage. It has however been demonstrated that the risk for white matter lesions is slightly increased in those with frequent (>5×) syncope [8].

20.2.1 Reflex Syncope

The signs and symptoms of vasovagal syncope can be divided into two groups: the first concerns the symptoms and signs due to retinal and cerebral hypoperfusion as described above. The second group is due to the underlying cause: an abnormal reflex of the otherwise normal autonomic nervous system. This ‘vasovagal’ reflex is characterised by vagally (parasympathetically) mediated bradycardia or even asystole with or without withdrawal of the sympathetically driven vasoconstriction. These changes in autonomic activity cause a specific set of signs and symptoms, labelled as ‘autonomic activation’, including perspiration, facial pallor, nausea, vomiting, and pupillary dilatation. Autonomic activation is often reported by younger subjects with VVS but less often by elderly, due to the inability to recall or identify these symptoms or due to mere absence of these signs in elderly.

Warning symptoms (including autonomic activation) start on average between 30 and 60 seconds before the actual onset of unconsciousness, but may vary between individuals. Sweating, pupillary dilatation, and deathly pallor are frequent early signs, but often difficult to observe in video recordings [4, 5]. Patients may be able to prevent actual syncope if they recognise these symptoms in an early stage and if they act immediately by sitting, squatting, or lying down. Counterpressure manoeuvres (e.g. leg crossing) are also effective to prevent further TLOC.

In some patients the BP stays low after the patient regained consciousness resulting in a recurring tendency to faint every time he or she is returned to the upright position (‘status vasovagalis’) [7]. A noticeable scarlet flush can occur after vasovagal syncope if the BP recovery was very rapid (cardioinhibitory VVS) but is also seen in those with an arrhythmogenic syncope [5].

Tilt-table testing (TTT) may be needed to establish a diagnosis of VVS; this requires provocation of typical complaints that are recognised by the subject or the eyewitness and coincide with an accelerating blood pressure (BP) decrease. Adding video to TTT has the advantage that clinical events can be studied in detail afterwards, as the complaints are often short-lasting. It also helps to gain more control over the test procedure. One could argue that the onset of EEG slowing should prompt to immediate tilt-back of the patient as it signifies severe hypoperfusion and will usually (if not counteracted) result in prolonged and severe LOC. Conversely, tilting back is not yet needed if the EEG is still normal despite seeming onset of clinical manifestations. A final advantage of adding video-EEG to TTT is that it

allows to study the relation between LOC and asystole as relying on heart rate alone is likely to overestimate the importance of asystole as the cause of syncope and result in unnecessary pacemaker implantations [9].

20.2.2 Orthostatic Hypotension

Orthostatic hypotension (OH) may cause syncope but often the core symptom is orthostatic intolerance with recurrent presyncope due to prolonged severe hypotension. Some presyncopal symptoms are unique for OH, such as the 'loss of ability to act'. This is a state in which patients are not unconscious but the BP is too low to think clearly but not low enough to cause unconsciousness. Eyewitnesses may notice a vacant look and an inability to respond but often these events go unrecognised especially those with comorbid movement disorders, e.g. Parkinson's disease. Another clinical feature specific to neurogenic OH is the 'coat hanger sign': pain in the neck radiating to the occipital region and shoulders caused by local ischaemia in upright position. Pain in the lower back, buttocks, and chest during orthostatic stress has also been described in OH but the underlying mechanism is unclear. All symptoms resolve when lying down. Transient ischaemic attacks (TIA) may occur during periods of hypotension, especially if the patient has carotid occlusive disease (hypotensive TIA).

TTT rarely induces syncope in OH. Therefore adding video and EEG has limited value in OH, although it may be helpful to demonstrate the 'inability to act'. If complaints occur they usually concern presyncope. In contrast to reflex syncope signs of autonomic activation are absent, especially in neurogenic OH. The symptoms are similar to that of gradual onset reflex syncope, but not exactly the same as in neurogenic OH where BP may remain low for prolonged periods without the patient losing consciousness.

20.2.3 Cardiac Syncope

Cardiac syncope can be caused by arrhythmias, structural heart disease, or disorders of the great vessels and cardiopulmonary disease (e.g. acute aortic dissection). Due to the abrupt onset of syncope, patients with arrhythmogenic cause of syncope usually experience no prodromes or a very short prodromal phase. Patients with a syncope secondary to structural cardiac, cardiopulmonary, and great vessel disease may however experience longer prodromal symptoms. These symptoms may relate to cerebral hypoperfusion or hint towards the underlying cause (shortness of breath, chest pain). The duration of the LOC strongly correlates with the duration of the cardiac standstill or loss of cardiac output. However, if the cardiac syncope is due to other causes the prodromal phase could be longer and patients could experience shortness of breath and angina pectoris. Recovery is marked by facial flushing if the circulation recovers rapidly, for example, in those with a transient AV block [1, 5].

20.3 Epileptic Seizures

Epileptic seizures are caused by an abnormal excessive or synchronous neuronal activity in the brain. The signs and symptoms in epilepsy are simply the result of the functions governed by the affected neurons meaning that the range of epileptic phenomena is practically that of the cortical functions. Only few seizure types may present as TLOC. The most frequent seizure type is the tonic-clonic seizure. This seizure type is subdivided according to the underlying cause. In those with focal epilepsy (e.g. epilepsy due to a brain tumour) they are labelled as ‘focal to bilateral tonic-clonic seizures’ whereas in those with generalised epilepsy (e.g. juvenile myoclonus epilepsy) they are labelled as ‘generalised tonic-clonic seizures’. Generalised tonic or atonic seizures may also present with TLOC but these seizure are extremely rare.

Tonic-clonic seizures could be misdiagnosed as reflex syncope, as motor phenomena also frequently occur in the latter. Nonetheless, the semiology differs between the two, one important feature is the number of jerks: fewer myoclonic jerks are seen in vasovagal syncope than in epileptic seizures. In this regard the ‘10/20 rule’ has been proposed [6]. There is a lack of in the overlap of the number of jerks between VVS and epileptic seizures; less than 10 jerks point towards reflex syncope whereas more than 20 jerks suggest a convulsive seizure.

In syncope patients, the motor phenomena start after onset of LOC, whereas in tonic-clonic seizures the jerks may start before the onset of unconsciousness. The presence of urine incontinence does not discriminate between syncope and seizures. A lateral tongue bite, a long period of postictal coma, or confusion are however strong clues favouring tonic-clonic seizures.

Ictal asystole is a rare clinical presentation where epileptic activity is the primary cause of syncope (see also Chap. 25). It is characterised by a sudden loss of tone during a focal, mostly temporal lobe, seizure with impaired awareness [10]. Ictal asystole is assumed to be self-limiting but may cause falls and injuries due to seizure-induced syncope. Proper trials are lacking, but retrospective studies suggest that improving seizure control may prevent ictal asystole.

20.4 Psychogenic Transient Loss of Consciousness

The presence or absence of pronounced limb and body movements during TLOC is the main difference between psychogenic non-epileptic seizures (PNES) and psychogenic pseudosyncope (PPS) (see Chap. 11). Patients with PNES or PPS also tend to be very suggestible explaining why TTT is often used for diagnosis. A brief explanation that the TTT may induce their symptoms is often enough to trigger a ‘positive’ outcome.

Adding video and EEG recordings are very important for the diagnosis PPS as they allow a certain differentiation between TLOC due to syncope and apparent unconsciousness due to PPS or PNES (EEG Class IIa recommendation in the American College of Cardiology syncope guideline and video and EEG Class IIb in

the European Society of Cardiology syncope guidelines) [1, 11]. Firstly, the video allows the identification of TLOC during TTT to be made afterwards. Without video, establishing the clinical presence of TLOC during PPS relies completely on the accurate recall of those present at the test. The recognition of TLOC requires assessment of loss of responsiveness, loss of normal motor control, and amnesia for the period of apparent unconsciousness. Adding video to the TTT allows the physician to study these events in more detail. Secondly, the presence of normal brain activity on the EEG recordings before, during, and after unresponsiveness helps to exclude TLOC due to syncope or epileptic seizures. One typical feature of psychogenic TLOC is that the eyes are virtually always closed during the episode, in contrast to VVS and epileptic seizures [12]. If the clinician proceeds to open the patient's eyes passively during the episode, there could be signs of active eye closure, i.e., apparent resistance to opening the lids, as well active aversion of gaze from the examiner. Passively lifted arms or legs may hesitate mid-air before falling down. The duration of the apparent unconsciousness is longer in patients with PPS compared to patients with VVS. In VVS, LOC rarely exceeds 1 min, while in PPS LOC may last several minutes or even hours. Falls, injuries, or incontinence are often seen as signs specific to epilepsy but may occur in psychogenic TLOC as well [13].

20.4.1 Psychogenic Non-epileptic Seizures

The presence or absence of pronounced movement during TLOC may guide the care pathway as those with motor phenomena will be referred to a neurologist, whereas those without such activity are more likely referred to any doctor treating TLOC. Misdiagnosed PNES patients may have serious consequences including unnecessarily prescribed high-dose antiepileptic drugs with potential for adverse effects and teratogenicity. Video and EEG registration of an event is required to reliably discriminate between PNES and epileptic seizures [14].

Movements that may be seen in PNES and which contrast with those in syncope or tonic-clonic seizures include waxing and waning jerks, pelvic thrusting, and tremors [3, 15, 16].

20.5 Equipment

Video

A high definition camera can be used to record the clinical signs during TLOC. The camera could be attached to the tilt table and move with it so that the changes in eyes, facial muscles, and upper body remain in view and are identified more easily. An additional video camera can be attached to the ceiling to trace movements in the lower body parts.

Video signals can be stored in the EEG machine, which in turn can be used to record together with the ECG and BP tracings.

EEG

In order to record a slow or slow-flat-slow pattern in syncope an EEG recording with a limited number [11] of electrodes is sufficient. The role of EEG in the diagnostic work-up of epilepsy is beyond the scope of this chapter.

20.6 Conclusion

Video recordings, both of spontaneous and provoked events, provide a crucial addition in the diagnostic work-up of TLOC. In true syncope, insufficient cerebral blood flow results in a range of symptoms and signs, such as light-headedness and visual disturbances; these may be seen in all forms of syncope. The severity and the duration of prodromal signs depends on the rate and the depth of the blood pressure drop. Syncope may be accompanied by additional semiological features that are unique to the cause of syncope. These include signs of autonomic activation (e.g. nausea and perspiration) in reflex syncope; coat hanger distribution pain or an inability to act in orthostatic hypotension and palpitations and symptoms of heart failure in some forms of cardiac syncope. Syncope has many overlapping symptoms and signs with tonic-clonic seizures and psychogenic TLOC. A detailed assessment of prodromal, ictal, and postictal signs may provide important diagnostic clues (Table 20.2).

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Table 20.2 Symptoms and signs before, during, and after loss of consciousness, including clues for specific causes

	Before LOC			During TLOC			After TLOC		
	Prodromal signs due to hypoperfusion	Other clues specific to cause	Fall	Movements	Number of jerks	Duration of TLOC	Eyes	Post ictal state	Other clues specific to cause
Reflex syncope (pre)syncope due to OH	Mostly present	Autonomic activation 'Coat hanger sign' 'Inability to act' TIA	Mostly flaccid fall – Rarely keeling over stiff	– Mostly asynchronous – Symmetric or asymmetric – Starts after onset of LOC	<10	<30 s	Nearly always open	Quick and complete recovery; disorientation <10 s	Flushing (in those with arrhythmia or cardioinhibitory VVS)
Cardiac syncope	Rarely present, only in those with gradual onset of syncope	Palpitations, symptoms of heart failure (e.g. dyspnoea)							
Tonic-clonic seizures	Not present	Focal seizure (e.g. impaired awareness) in those with focal epilepsy Generalised seizure (e.g. myoclonus) in those with those with generalised epilepsy	Tonic phase epilepsy; keeling over stiff	– Mostly synchronous – Symmetric or asymmetric – Starts before or after onset of LOC	>20	Mostly up to 1 min but may last longer		Confusion, comatose, or immediate sleep	Lateral tongue biting (rarely bilateral)
Psychogenic TLOC	Not present	No specific clues	Mostly flaccid fall	– PPS; absent – PNES – Symmetric or asymmetric – Asynchronous, waxing and waning – Pelvic thrusting – Tremor	Any number	Mostly long duration (several min)	Mostly closed	Quick and complete recovery possible	Emotional (crying); stuttering speech, trembling

Abbreviations: *TLOC* transient loss of consciousness, *s* seconds, *PPS* psychogenic pseudosyncope, *PNES* psychogenic non-epileptic seizures

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Part V

Treatment Considerations

Chapter 21

Indications for Pacing in Patients With Unexplained Syncope and Bifascicular Block



Oscar Oseroff and Nestor O. Galizio

21.1 Introduction

Bifascicular block is defined as complete left bundle-branch block or complete right bundle-branch block with left anterior hemiblock or left posterior hemiblock (QRS > 120 ms).

Bifascicular block is associated with increased mortality, mainly due for sudden cardiac death [1, 2].

Syncope is a frequent event in patients with bifascicular block. The underlying causes are heterogeneous, the most frequent being intermittent high-degree AV block or neurally mediated reflex syncope. Several studies of follow-up in bifascicular block patients with previous syncope reported consistent rates of need for temporary or permanent AV block development over time [3–5].

Patients with bifascicular block and both history of previous syncope and a negative EPS (HV < 70 ms and no induction of ventricular tachyarrhythmia) have been the subject of several investigations involving pacemakers or loop recorders to identify the nature of associated syncopal recurrences and its most appropriate treatment [5–8].

In the past, Guidelines have given a class II-A recommendation for pacemaker implantation in patients with bifascicular block and syncope of apparently unexplained origin, to avoid the risk of syncopal recurrences and potential physical trauma [9–12].

The PRESS study was designed to assess the role of dual chamber pacing in preventing symptom recurrences in bifascicular block patients [13]. The study included 101 patients with bifascicular block and a history of syncope of unknown origin, all underwent ECG, Holter monitoring, tilt test, carotid sinus massage, and EPS to rule out any possible identifiable cause of syncope. These patients had indications for permanent

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pacing according to 2002 ACC-AHA-HRS guidelines (class II-A). Device programming mode (NASPE/BPEG code) at DDD with a lower rate of 60 ppm (DDD-60) was compared with backup pacing at DDI with a lower rate of 30 ppm (DDI-30).

The end point consisted of: syncope, symptomatic presyncopal episodes associated with a device intervention (ventricular pacing), and symptomatic episodes associated with intermittent or permanent atrioventricular block (any degree).

Primary end point events at 2 years were observed in 23 patients, with a significant lower incidence in the study group (hazard ratio, 0.32; 95% confidence interval [CI], 0.10–0.96; $P = 0.042$). Reduction of any symptoms, associated or not with device intervention, was superior in DDD-60 compared with DDI-30 (hazard ratio, 0.4; 95% confidence interval, 0.25–0.78; $P = 0.0053$). Fourteen patients developed other rhythm diseases and met class I indication for pacing. The annual incidence of rhythm disease development was 7.4% [13].

The 2017 ACC/AHA/HRS guidelines for the evaluation and management of patients with syncope put forward recommendations for EPS and treatment of syncope [13].

EPS has a limited role in the evaluation of syncope, especially in patients without heart disease or with low suspicion of an arrhythmic etiology [14, 15]. The guidelines have no recommendations about bifascicular block and EPS.

A search and review of papers on syncope and bradycardia has been performed since the last updated guidelines were published in 2012 [10, 12]. The writing committee supports the previous recommendations for patients with syncope and chronic bifascicular block but without documented high-degree AV block, having excluded other causes for the AV block. (Class I Level C- EO) [13]

According to the 2018 ESC Guidelines for the diagnosis and management of syncope [12], patients with bifascicular block and syncope are at risk of developing high-degree AV block [1]. During EPS a prolonged HV interval ≥ 70 ms, or the induction of second- or third-degree AV block by pacing or by pharmacological stress (ajmaline), identifies a group at higher risk of developing AV block [15–17].

However, approximately one-third of patients with a negative EPS in whom an ILR was implanted developed intermittent or permanent AV block on follow-up [18]. Thus, EPS has a low negative predictive value. For these reasons, the ESC Guidelines justified an upgrade of the recommendation for EPS-Guided therapy (cardiac pacing), in patients with a positive EPS, from class IIa to class I.

Empirical pacing is not advised in patients with bifascicular block but without evidence of prolonged HV or intermittent AV block. Pacing without documentation of AV block exposed patients to the risk of recurrence of syncope in about one-quarter of cases during long-term follow-up and was unnecessary in the other half [13, 19]. Thus, only one in four pacemakers will finally be appropriate. The above considerations justify a class IIb indication in the ESC Guidelines for pacing [20].

To overcome the above problems, ESC Guidelines on pacing [20] in patients with LVEF $>35\%$ recommend a strategy of EPS followed by ILR if the EPS findings are unremarkable. With this strategy, a pacemaker was implanted in approximately half of the patients and these patients had syncope recurrence in 0–7% of cases [19, 21]. Nevertheless, the Task Force recognizes that in the “real world,” an

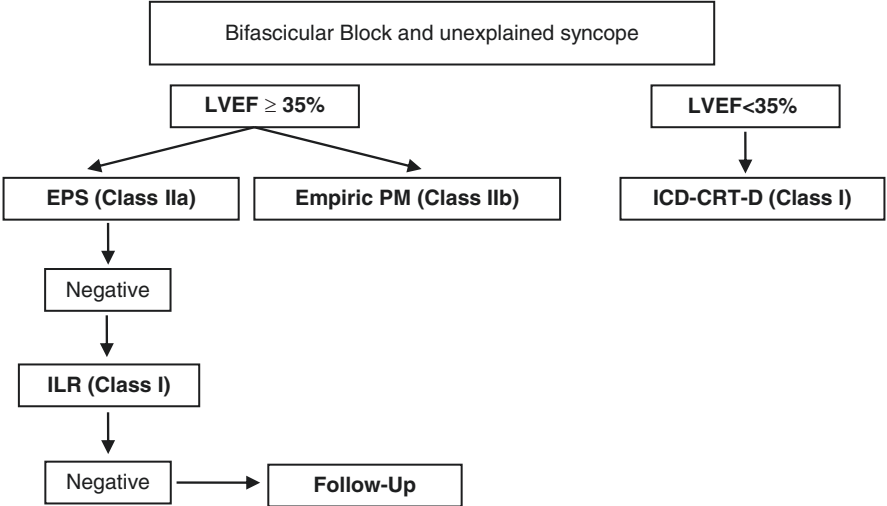


Fig. 21.1 Bifascicular Block and unexplained syncope

empirical pacemaker may be acceptable in selected patients at high risk of traumatic recurrence (e.g., elderly or frail patients with unpredictable syncope) and that an individual risk–benefit evaluation is warranted.

A high incidence of total deaths (about one-third sudden) was observed in patients with bifascicular block and previous myocardial infarction, heart failure, or low ejection fraction [22–24]. The high total number and incidence of sudden mortality seems mainly to be related to the underlying structural heart disease and ventricular tachyarrhythmias. Syncope is a symptom and risk factor, rather than the cause of death [25]. Unfortunately, ventricular programmed stimulation does not seem to identify these patients. Therefore, an implantable cardioverter defibrillator (ICD) or a cardiac resynchronization therapy defibrillator (CRT-D) is indicated in patients with bifascicular block, previous myocardial infarction, congestive heart failure, or/and depressed systolic function ($EF < 35\%$) for the prevention of SCD.

The strategy for the management of patients with unexplained syncope and bifascicular block is summarized in Fig. 21.1.

21.2 Conclusions

The currently published practice guidelines recommend a strategy of EPS followed by ILR if the EPS findings are unremarkable in patients with $LVEF > 35\%$. In patients with bifascicular block and low ejection fraction ($EF < 35\%$) an ICD or CRT-D is indicated for the prevention of SCD.

Nevertheless, the Task Force recognizes that an empirical pacemaker may be acceptable in selected patients at high risk of traumatic recurrence (elderly or frail

patients with unpredictable syncope) with bifascicular block and unexplained syncope without documented high-degree AV block, having excluded other causes for the AV block.

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Chapter 22

Unexplained Syncope in Patients with High Risk of Sudden Death



David S. Cannom

22.1 Introduction

Over the last 30 years there has been remarkable interest among cardiologists in the evaluation and treatment of patients with syncope. This has led to many important clinical studies and an abundant literature. The European Society of Cardiology began publishing guidelines for the management of syncope in August 2001. These guidelines defined the various types of syncope (neurally mediated, orthostatic, cardiac arrhythmias, and syncope related to structural heart disease). In 2009 the European Society of Cardiology expanded their guidelines into an excellent document of over 50 pages. For the first time the syncope guidelines used a traditional guideline format in which experts made judgments based on the class of the recommendations (Classes 1–3) and level of evidence (A–C). This format put syncope guidelines on a par with other specialty guidelines and showed that the study of syncope had come of age.

In 2018 the European Society of Cardiology updated their guidelines and in 2017 the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society collaborated on their syncope guidelines [1, 2]. Both sets of guidelines cover every aspect of syncope and when read closely are remarkably similar. In this chapter we will attempt to synthesize the current recommendations of both sets of guidelines, and also discuss the minor differences between the two sets of guidelines (noting that the 2018 ESC document makes frequent reference to the 2015 ESC Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Death) [3].

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22.2 Classification of Syncope

Both the ESC guidelines and the ACC/AHA/HRS guidelines place appropriate emphasis on the importance of a detailed history and physical in diagnostic evaluation of a patient who presents with presumed syncope in whom other non-syncope causes of collapse have been excluded. Potential causes of loss of consciousness which are not due to syncope include (among other things) seizures, a forgotten trip and fall accident or concealed drug use.

The history should focus on the situation in which the syncope occurs and include careful documentation of prodromal symptoms that might point to an autonomic cause, bystander observations of the event, vital signs both lying and standing, and post-event symptoms. Comorbidities, medication, and any known evidence of cardiovascular disease are important. A family history of possible sudden death should be obtained.

What have we learned in the last 40 years about types of syncope? Not all syncopal spells are the same [2]. Low risk patients are those whose syncope is consistent with a history of autonomic dysfunction with vagal nerve excess causing syncope. Such environmental causes of reflex syncope include sudden unexpected sights, sounds, smell or pain. A heavy meal followed by abruptly standing is a common cause of vagal excess. Such patients usually fall to the ground gradually with syncope and do not experience physical harm. These patients are also younger, do not usually have known cardiac disease, and are commonly women: such patients have experienced multiple, similar episodes during their lifetime. The patient is usually not anxious when he or she wakes up (Table 22.1).

Table 22.1 Historical characteristics associated with increased probability of cardiac and noncardiac causes of syncope

More often associated with cardiac causes of syncope
<ul style="list-style-type: none">• Older age (>60 years)• Male sex• Presence of known ischemic heart disease, structural heart disease, previous arrhythmias, or reduced ventricular function• Brief prodrome, such as palpitations, or sudden loss of consciousness without prodrome• Syncope during exertion• Syncope in the supine position• Low number of syncope episodes (1 or 2)• Abnormal cardiac examination• Family history of inheritable conditions or premature SCD (<50 years of age)• Presence of known congenital heart disease
More often associated with noncardiac causes of syncope
<ul style="list-style-type: none">• Younger age• No known cardiac disease• Syncope only in the standing position• Positional change from supine or sitting to standing• Presence of prodrome: nausea, vomiting, feeling warmth• Presence of specific triggers: dehydration, pain, distressful stimulus, medical environment• Situational triggers: cough, laugh, micturition, defecation, deglutition• Frequent recurrence and prolonged history of syncope with similar characteristics^a

^aShen et al. [2]

High risk patients who experience syncope commonly have known heart disease often with a reduced ejection fraction, are male and usually over 60 years old. The episode of syncope in this population occurs abruptly, often during physical exertion, and are few in number during a life time. The patient usually hits the ground with force enough to cause injury. When the patient awakens he is frightened and wonders what has happened. In the 1980s the insightful teaching of well-known electrophysiologist Dr. Masood Akhtar of Milwaukee was that if a patient with heart disease has syncope, it is due to an arrhythmia until proven otherwise.

Syncope is difficult to evaluate as there are both differences between how patients describe syncope as well as unknown contributors to the symptoms such as drugs or alcohol. Marked light-headedness or dizziness without losing consciousness is not true syncope. With experience, clinicians become better at distinguishing the various types of syncope. It takes extra time and effort to consider the many possible causes of syncope especially when knowing that making a soft call of cardiac syncope can lead to an unwarranted ICD.

22.3 ICD Therapy for the Syncope Patient

The first ICD was implanted in 1981 at Johns Hopkins Hospital in a patient with two prior cardiac arrests. A series of randomized trials were initiated by cardiologists, funded by industry and the ICD was approved by the FDA for clinical use. The patient group that benefits most from the ICD has a cardiomyopathy either ischemic or non-ischemic and an ejection fraction of $<35\%$. No risk stratifier other than a low ejection fraction identifies a high risk patient. Much basic and clinical work has sought other clinical risk factors that might help distinguish patients at risk for sudden death from those dying of nonsudden death. The population of patients who qualify for an ICD remains a large one but can be diminished by the aggressive use of best medical therapy and cardiac resynchronization devices as was indicated in the Danish Trial [4].

Many patients with genetic heart disease are at high risk for sudden death but there have been no randomized clinical trials to give scientific evidence of ICD superiority over medical therapy. Useful clinical risk stratifiers beyond syncope have been developed in patients with hypertrophic cardiomyopathy (see below) but less so in patients with Brugada syndrome or arrhythmogenic right ventricular cardiomyopathy. Long QT patients are successfully treated based on the degree of QT lengthening in association with syncope thought to be cardiac in origin.

22.4 Impact of Syncope in the Cardiomyopathy Patient and Its Relationship to Sudden Death

Syncope was shown to be a marker for future sudden death in the SCD-HeFT trial suggesting that an episode of syncope in the cardiomyopathy patient indicates a more fragile myocardial substrate than that present in similar cardiomyopathy patients without syncope. Syncope in the SCD-HeFT trial helped define a patient subgroup with an unstable, end stage cardiomyopathic process that increases risk of sudden death [5].

Another study with similar findings is the Multicenter Automatic Defibrillator Implantation Trial (MADIT-RIT) published in 2014 [6]. This 1500 patient trial randomized ICD patients to one of the three different first shock programmed therapies. Group A was routine “out of the box” ICD programming which has been employed in devices for decades and delivers a shock when a 170 beat/min rate ventricular tachycardia is sensed. Group B programming did not deliver a shock until the sensed tachycardia was rapid at 200 beats/min. Group C programming employed sensed VT at 170 beats/min but delayed first therapy for 60 s as many ventricular tachycardias terminate spontaneously before 60 s.

The MADIT-RIT trial design was to determine whether aggressive ICD programming (Group B and Group C patients) in a large patient population could reduce the number of unnecessary shocks over time. Patient syncope was a prespecified safety end point in the trial as there was concern on the part of the investigators that either high-rate cutoff or delayed therapy (Group B and Group C patients) could cause a syncopal spell before therapy was delivered. During a mean follow-up of 1.4 years \pm 0.6 years a total of 64 patients experienced at least 1 syncopal spell. Syncope occurred equally in all three treatment arms with 21, 22, and 21 patients experiencing syncope in arms A, B, and C, respectively. Defined by employing device telemetry the study determined that 21 patients had syncopal events (33%) that were caused by VT or VF in contrast to 39 patients with syncopal events (61%) that were classified as nonarrhythmogenic without an ICD shock delivered during the syncopal spell. Both arrhythmic and nonarrhythmogenic syncope were significantly associated with a subsequent increased risk of death (Table 22.2). Baseline variables

Table 22.2 Distribution of syncope according to cause by ICD programming/treatment arm in MADIT-RIT study

	Total	A: conventional	B: high-rate cutoff	C: delayed therapy
Arrhythmogenic	25 (39%)	8	7	10
Supraventricular	1	1	0	0
Ventricular tachycardia	15	3	4	8
Ventricular fibrillation	6	3	2	1
Other	2	0	1	1
Undetermined arrhythmia	1	1	0	0
Nonarrhythmogenic	39 (61%)	13	15	11
Vasovagal	11	2	7	2
Structural heart disease	1	1	0	0
Orthostatic hypotension	14	7	3	4
Neurological/epilepsy	1	0	1	0
Metabolic	1	0	1	0
Unknown cause (not arrhythmic)	11	3	3	5
Total all-cause syncope ^a	64	21	22	21

No significant difference was found for risk of all-cause, arrhythmogenic, or nonarrhythmogenic syncope when the 3 programming/treatment arms were compared. ICD indicates implantable cardioverter defibrillator. Non arrhythmogenic syncope was associated with episodes of decreased blood pressure

^aRuwald et al. [6]

associated with arrhythmogenic syncope were an underlying ischemic cardiomyopathy and previous ventricular arrhythmias. No clinical variables or a history of prior ICD shocks explained the increased risk of death in the patients experiencing nonarrhythmogenic syncope without an ICD shock which suggests a multifactorial cause.

This MADIT-RIT findings support the observations mentioned above in the SCD-HeFT data which demonstrated that syncope in some heart failure patients represents an inability to compensate for hemodynamic collapse and becomes a marker for death even in the absence of an arrhythmia.

The European guidelines recognize that unexplained syncope in a patient with structural heart disease or inheritable arrhythmia syndromes imposes an increased risk of sudden death. These European syncope guidelines state that “unexplained syncope is defined as syncope that does not meet any Class 1 diagnostic criterion defined in the tables of recommendations for an ICD in the guidelines” (ESC guidelines p 1825). The guidelines go on to recommend that an ICD be considered in patients with unexplained syncope and systolic impairment who are without a current indication for an ICD. No data is given regarding the range of ejection fraction included in this recommendation and this author assumes it could include patients not currently covered in guidelines such as an ischemic patient with an EF of over 35%. This is a Class IIa recommendation. This attention in the guidelines to this newly defined category of syncope is one of the most important contributions of the 2018 ESC guidelines. It gives clinicians greater flexibility in recommending an ICD for patients who are thought to be at high risk for sudden death but are without a defined indication in the guidelines.

22.5 Arrhythmic Conditions with Underlying Structural Disease

22.5.1 Hypertrophic Cardiomyopathy (HCM)

HCM can present in a number of ways including sudden cardiac death, atrial fibrillation, and congestive heart failure, depending upon the patient’s age. However, the overall annual cardiovascular mortality in HCM is low (about 1–2% per year).

The earliest work to define the risk of sudden death in HCM was published in 2006 by Elliott et al. [7]. This paper showed that syncope was the major predictor of sudden death in HCM. Other clinical conditions including a family history of sudden death, massive (>3 cm) left ventricular wall thickness, nonsustained VT and blood pressure drop with exercise are also risk factors for SCD.

SCD risk incidence is highest in the asymptomatic or mildly symptomatic patient less than 30 years old. The high prevalence of HCM of 1:500 in the general population makes risk stratification in this population a relatively common clinical challenge.

A recently published series of 1000 HCM patients who have been followed for over 20 years by a single group emphasizes that clinicians must make optimal use

of ICDs, indicated medication, septal myectomies, aggressive treatment of atrial fibrillation (AF) and, when indicated, cardiac transplantation. These modalities have reduced HCM related death in this population from 5% to 1.5% per year [8]. In this group of patients, 389 patients received an ICD and 40 patients had appropriate ICD therapy during follow-up.

Syncope is associated with a two-fold risk of sudden death in HCM [1]. The patient over age 40 with remote episodes of syncope clinically presenting with vasovagal-like symptoms does not require an ICD. Other causes of syncope in HCM patients include arrhythmia (usually rapid AF) and a primary hemodynamic mechanism usually due to LV outflow tract obstruction. These causes can usually be identified and treated medically or surgically without an ICD.

The risk stratification protocol for HCM in the US guidelines is relatively easy to use and has been effective in reducing sudden death [9]. There is a consensus among experts that of the potential risk factors for sudden death in HCM, that BP drop with exercise and nonsustained VT are less important risk factors than syncope, family history, and LV wall thickness. A positive gadolinium scan has shown to further select a group at high risk for SCD although such patients are small in number among those with HCM.

There is an important difference between the European and AHA/ACC/HRS guidelines regarding risk stratification in HCM patients. The US guidelines state that a HCM patient with syncope should receive an ICD as a Class 1A recommendation. US guidelines state that there is no new data in the literature that would change the similar recommendation in 2011 US guidelines. By contrast, the ESC has developed a sophisticated risk stratification methodology to identify high risk patients. These factors include age, family history for sudden death, maximum left ventricular wall thickness, left atrial diameter, and nonsustained VT. In this new approach, an HCM patient with arrhythmic syncope and HCM will receive an ICD as a Class 1B recommendation. However, patients with recurrent episodes of unexplained syncope who are at low risk by the SCD score are recommended to have a loop recorder implanted for long-term monitoring.

The concern from US investigators is that most HCM patients with SCD or appropriate ICD shocks are misclassified as “low risk” using the ESC risk stratification methodology and will not receive an ICD. Maron and colleagues tested the ESC risk score against a large (1629 patients) independent HCM cohort which had been risk stratified based on US guidelines and found the ESC risk score to be unreliable for predicting future SCD events in individual patients [10]. This latter concern needs to be tested by a review of the Maron data by the ESC to better align the two sets of guidelines.

22.5.2 Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Over the last 45 years an enormous amount of clinical work has clarified the clinical features of ARVC in a precise fashion. The number of genes causing the entity has expanded to at least 13 and inheritance has been outlined. The Johns Hopkins group

and others have described the adverse effect that moderate to intense exercise has on the ARVC clinical course [11]. The disease is associated with sudden death in young patients, especially athletes.

The ACC/AHA/HRS guidelines recommend ICD implantation in ARVC patients who present with syncope of suspected arrhythmic etiology as a Class IIa indication. The diagnosis and risk stratification of ARVC patients is complicated enough that a randomized trial to assess the role of the ICD is not yet possible.

The European 2018 guidelines state that ICD implantation may be considered in patients with ARVC and a history of unexplained syncope. However, the recommendation is a weak Class IIb recommendation. The uncertainty of the authors about this recommendation is apparent. The 2018 guidelines ask the reader to consider other known risk factors for clinical events including frequent nonsustained ventricular tachycardia, a family history of premature death, extensive right ventricular disease, marked QRS prolongation, late gadolinium enhancement on MRI, left ventricular dysfunction, and VT induction during electrophysiologic study. Some or all of these factors considered critically might make the recommendation more enthusiastic (Fig. 22.1).

The ESC 2018 syncope guidelines refer the reader to the 2015 ESC guidelines on ventricular arrhythmias and sudden death in which there was also ambiguity about ICD implantation in ARVC. The 2015 ESC ventricular arrhythmia document states that “studies examining outcomes in ARVC are so diverse that recommendations on ICD therapy for primary care are challenging” [3]. The 2015 Ventricular Arrhythmias guidelines list reservations for device therapy but do not make a numerical recommendation. In the 2018 ESC Syncope guidelines an ICD is recommended as Class IIb recommendation for an ARVC patient with syncope but with no literature cited

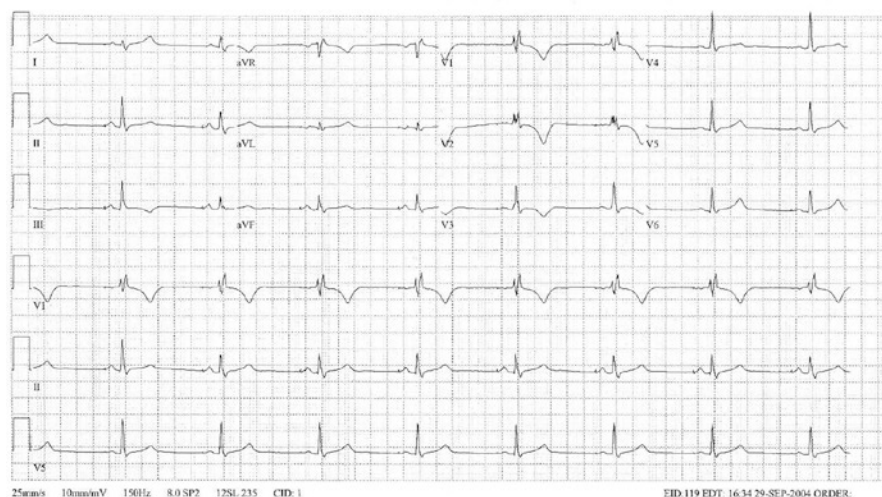


Fig. 22.1 ARVC: This is the EKG of a 31 years old woman with ARVC. She presented with sustained ventricular tachycardia and received an ICD. The diagnosis of ARVC was made by a right ventriculogram and a cardiac biopsy. She had multiple shocks and a VT ablation was successful. She is now on sotalol 200 mg/day. She has a full time job and walks every day

beyond the ESC 2015 Ventricular Arrhythmia Guidelines. In contrast, the 2018 ESC guidelines recommend an ILR as a Class IIa recommendation for the syncopal ARVC patient rather than an ICD.

The difference between the European and US guidelines recommendations regarding an ARVC with syncope will be difficult to resolve until large clinical outcomes in risk stratification are published. This difference also points out that in Guidelines development honest differences between two approaches need to be respected. The reproducibility and precision of the HCM data on clinical outcomes seems simple compared to ARVC which has variability in its genetics, anatomy, and clinical presentation.

22.5.3 Long QT Syndrome

Long QT syndrome is characterized by a prolonged QT interval and ventricular arrhythmias triggered by adrenergic stimulation. Long QT is diagnosed with a QTc of 480 ms in repeated ECGs or risk score (pioneered by Schwartz) of >3 [12]. In the presence of unexplained syncope a QTc of >460 ms is sufficient to make a diagnosis. The average patient presents at age 14. The annual rate of sudden death in untreated long QT patients is estimated to be between 0.33 and 0.9%, whereas the annual risk of syncope in long QT patients is estimated to be 5% [13]. Patients with the diagnosis of long QT should maintain normal electrolyte levels and avoid medications that prolong the QT interval. Patients should avoid genotype-specific triggers for arrhythmias which include strenuous swimming in LQT1 and exposure to loud noises in LQT2. No disease process in clinical cardiology comes closer to delivering precision therapy to affected patients than in the long QT syndrome.

Seventeen genes have been associated with long QT syndrome and to date have been identified to cause at least 19 phenotypes. The response to beta blocker therapy is greater among LQT1 patients compared to LQT2 and LQT3 patients. Of the beta blockers, nadolol has been the preferred drug used by the largest LQTS referral centers over the past 25 years [14]. If the patient has a prolonged QTc, a beta blocker is begun even if the patient is asymptomatic.

If the patient presents after a cardiac arrest, an ICD is recommended, and a beta blocker is typically also added to prevent frequent shocks. Survivors of a cardiac arrest have a high risk of recurrence even when receiving a beta blocker. The occurrence of a syncopal event in a long QT patient is associated with an increased risk of a cardiac arrest and is an indication for an ICD [15]. This is considered a Class IIa indication in both the ESC and AHA/ACC/HRS guidelines. The European guidelines state that in a patient with recurrent syncopal spells on a beta blocker consideration could be given to an ILR if the patient is at low risk. This recommendation is a Class IIa. The European guidelines also state that LQTc3 patients should not be given beta blockers (Fig. 22.2).

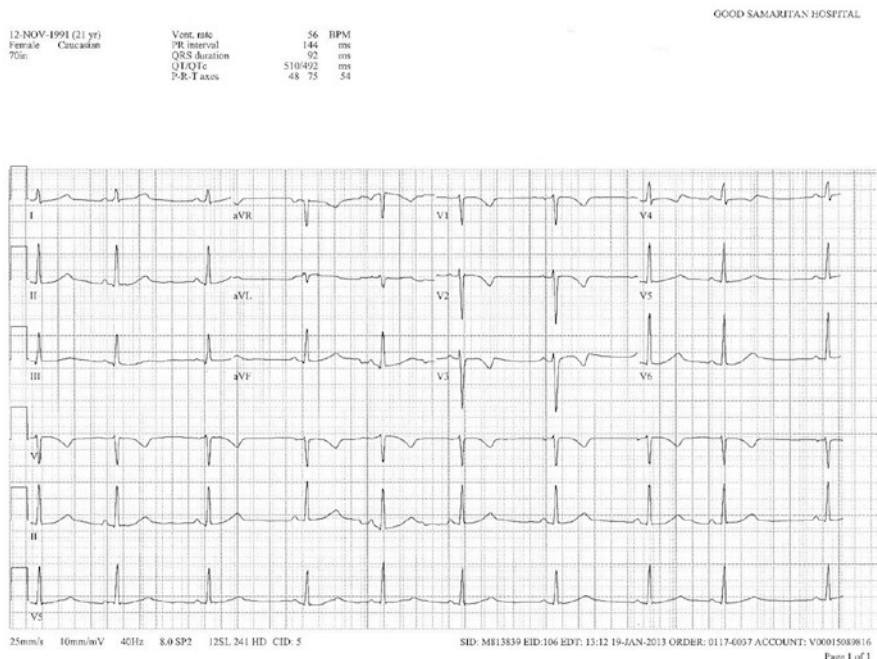


Fig. 22.2 Long QT Syndrome: This is the EKG of a 21-year-old female with a QTc of 490 and a strong family history of sudden death. She has the KCNH2 gene which is diagnostic of long QT 2. She has an ICD and has had no shocks on a beta blocker

Many clinicians think that there is a tendency to overuse ICDs in long QTc patients. The guidelines now are quite conservative in recommending ICDs in long QT patients without a cardiac arrest. Most young patients without high risk long QT can be started on beta blockers and with an ICD recommended only if they have syncope or cannot take beta blockers. A thorough discussion with the long QT patient, his or her family and the attending regarding ICD implantation versus a beta blocker is critical in this at risk population.

22.5.4 Brugada Syndrome

Usually a typical ECG pattern leads to the diagnosis of type I Brugada Syndrome. However, true Brugada ECG abnormalities can be difficult to separate from many other conditions that produce Brugada phenocopies, but are more benign.

There are 12 genes associated with the Brugada syndrome but only SCN5A and CACNA1C account for most gene positive patients and families. Genetic testing is helpful in making the diagnosis of Brugada syndrome but does not affect prognosis. The prevalence of Brugada syndrome appears to be higher in the Far East than in Western countries (Fig. 22.3).

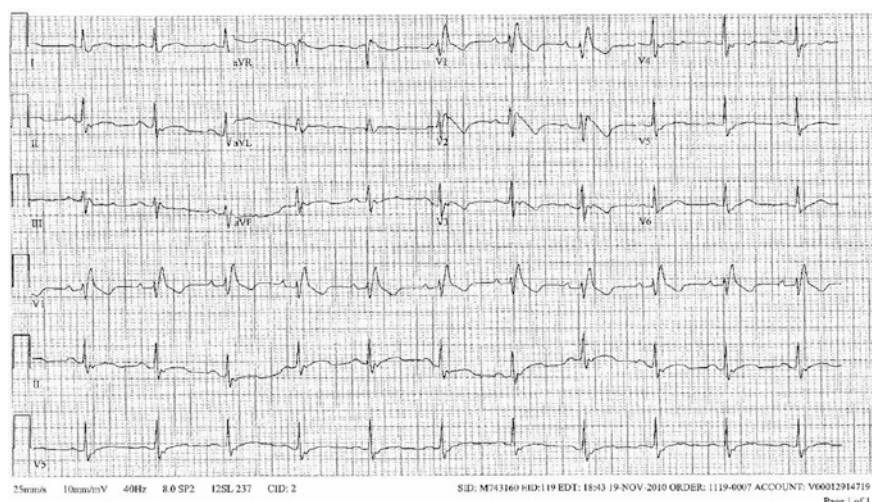


Fig. 22.3 Brugada Syndrome: This is the EKG of a 62-year-old male with a history of atrial fibrillation. He had symptoms of dizziness but not syncope. He was seen by an electrophysiologist in 2010 and admitted for an AF ablation. On EKG he had type 1 Brugada syndrome. He underwent an ablation and an ICD implantation. He has not had a device discharge in the past 9 years. There was no history of syncope or family history of Brugada syndrome. An ICD would not be recommended in this era

The average age of a first VF episode in Brugada patients is 41 years but VF can occur at any age, and usually occurs during rest or sleep. Fever, large meals, and excessive alcohol can unmask a type 1 Brugada ECG.

The Finger Registry of 1029 patients with a mean age of 45 years and a Brugada ECG showed that at a median follow-up of 31.9 months the cardiac event rate per year was 7.7% (most of these patients experienced an ICD shock (86%) and only 7 patients died suddenly). The cardiac event rate was 1.9% in those patients with syncope, and only 0.5% (2 patients) in patients who were asymptomatic. The presence of an SCN5A gene, family history sudden death or a positive EP study were not predictors of arrhythmic events [16].

There is a consensus between the ESC and AHA/ACC/HRS guidelines that in a Type 1 Brugada patient a history of syncope thought consistent with an aborted ventricular arrhythmia is a Class IIa indication for an ICD. The European guidelines go on to state that a patient with unexplained syncope thought not to be caused by an arrhythmia is a Class IIa candidate for a loop recorder.

There are areas of uncertainty in the guidelines which mirror the current difficulty generalizing a clinical approach to these patients. The AHA/ACC/HRS guidelines state that the value of EPS in assessing the mechanism of syncope is unknown and this procedure has a Class IIb recommendation. They state that the role of inducibility remains controversial in patient selection.

22.5.5 *Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)*

CPVT is a rare inheritable arrhythmic disorder that is characterized by adrenergically mediated polymorphic tachycardias in patients with no structural heart disease and a normal electrocardiogram. The QT interval is normal in these patients and shortens normally with exercise. The rhythms induced are exercise or emotional-induced polymorphic VT or bidirectional VT. Genetic testing can be critical to make a diagnosis of CPVT. A number of genes are associated with CPVT but the two most common genes are RYR2 and CASQ2 [16].

The clinical presentation is typically in children or young adolescents. The entity can be confused with epilepsy or long QT syndrome. Often there is a family history of sudden death, aborted cardiac arrest or epilepsy. The prevalence of CPVT is estimated to be 1 in 10,000. Provocative testing using exercise testing exposes the arrhythmia which increases from ventricular premature beats to polymorphic couplets or nonsustained (often “bidirectional”) VT [17]. Holter monitoring can be used with the patient encouraged to exercise. In the adult patient HCM, CAD, or ARVC is considered and can be excluded by cardiac imaging techniques and genetic testing.

When a diagnosis is made medical therapy is begun at once using a beta blocker and adding flecainide if necessary. If the CPVT patient has had a cardiac arrest or recurrent syncopal spells an ICD is recommended with a beta blocker. If recurrent syncopal spells occur or polymorphic or bidirectional VT occurs, flecainide should be considered in addition to a beta blocker. The presence of any provokable ventricular arrhythmias on a treadmill are an indication to add flecainide to a beta blocker. Flecainide also has a role in preventing ventricular tachycardia induced shocks in a patient with an ICD. If an ICD is implanted, flecainide and beta blockers should be intensified to minimize spurious shocks. Aggressive ICD programming including high-rate cutoffs and prolonged sensing before a shock is recommended.

The ACC/AHA/HRS guidelines do a very careful job in outlining therapy for this difficult patient group. The recommendation regarding ICD therapy including patients with a history of cardiac arrest, recurrent syncope or polymorphic bidirectional VT despite optimal therapy is a Class Ia indication. The recommendations regarding intensive medical therapy are Class IIa indications. The ESC’s guidelines did not address CPVT in this set of guidelines and refer the reader to the 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden death (Table 22.3).

22.6 A Clinicians Observations on the ACC/AHA/HRS and ESC Syncope Guidelines

The following provides a list of observations that are supported by clinical observation and for the most part by practice guidelines;

1. The 2017/2018 syncope guidelines of the ESC and ACC/AHA/HRS are conservative regarding ICD usage; they are also very similar.

Table 22.3 Indications for an ICD in patients with unexplained syncope and a high risk of SCD (based on the recommendations of the 2017 ACC/AHA/HRS guideline for the evaluation and management of syncope and the 2018 ESC guidelines for the diagnosis and management of syncope)

Clinical situation	ACC/AHA/HRS	ESC guidelines
Patients with ischemic and nonischemic cardiomyopathy with ejection fraction <35% and heart failure	Ia	Ia
Patients with unexplained syncope with systolic impairment but without a current indication for an ICD		II
Hypertrophic cardiomyopathy in patient with syncope	Ia	Special ESC HCM Risk score
Arrhythmogenic right ventricular cardiomyopathy	IIa	IIB
Long QT syndrome	IIa	IIa
Brugada syndrome	IIa	IIa
Catecholaminergic polymorphic ventricular tachycardia	IIa	Not addressed

- Careful definitions of arrhythmic syncope and nonarrhythmic syncope help support clinical decision making. The current guidelines take a strong position on the importance of this concept.
- The disease states discussed in the syncope guidelines are different from ICD and CRT guidelines and are not based on clinical trials currently. This absence of clinical trial data has not substantially affected our treatment of HCM and long QT patients and the large Brugada and HCM registries make randomized trials less important.
- We are better at predicting clinical features that are predictors of a poor outcome in HCM and long QT: ARVC is most difficult.
- The role of EPS is modest in these guidelines.
- There is as yet no consideration in the guidelines on use of the S-ICD. However, this will inevitably change as the early S-ICD papers include patients with genetic heart disease.

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Chapter 23

Non-Pharmacological and Pharmacological Therapies in Vasovagal Syncope: Current Status



Payam Pournazari and Satish R. Raj

23.1 Introduction

Vasovagal syncope (VVS) is a non-life-threatening disorder, and in most patients pharmacological treatment is not required. However, patients with recurrent episodes of syncope, and especially those suffering from prior injuries, are likely to have impaired quality of life. Drug therapies are appropriate for these patients. Despite numerous efforts and trials, therapeutic options in patients with VVS are very limited; there are no pharmacological treatments that have convincingly been shown to be effective in large clinical trials.

Education and lifestyle modifications remain the cornerstones of therapy for patients with VVS at this time [1]. Many patients with VVS will experience a reduction in the number of syncopal episodes after being started on any medical therapy, despite variable efficacy of the therapy. This makes it more challenging to show the benefits of medical therapies in patient with VVS [2].

Three leading professional organizations have issued position statements or guidelines in the last 5 years that address the management of VVS. In this chapter, we will highlight the specific recommendations of the Heart Rhythm Society (HRS) 2015 Expert Consensus Statement [3], the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) 2017 Syncope Guidelines [4], and the European Society of Cardiology (ESC) 2018 Syncope Guidelines [1]. We will review recommendations to discontinue blood pressure lowering medications, the use of non-pharmacological therapies and approaches, and then the status of commonly used pharmacological approaches. An evaluation and treatment algorithm is shown in Fig. 23.1.

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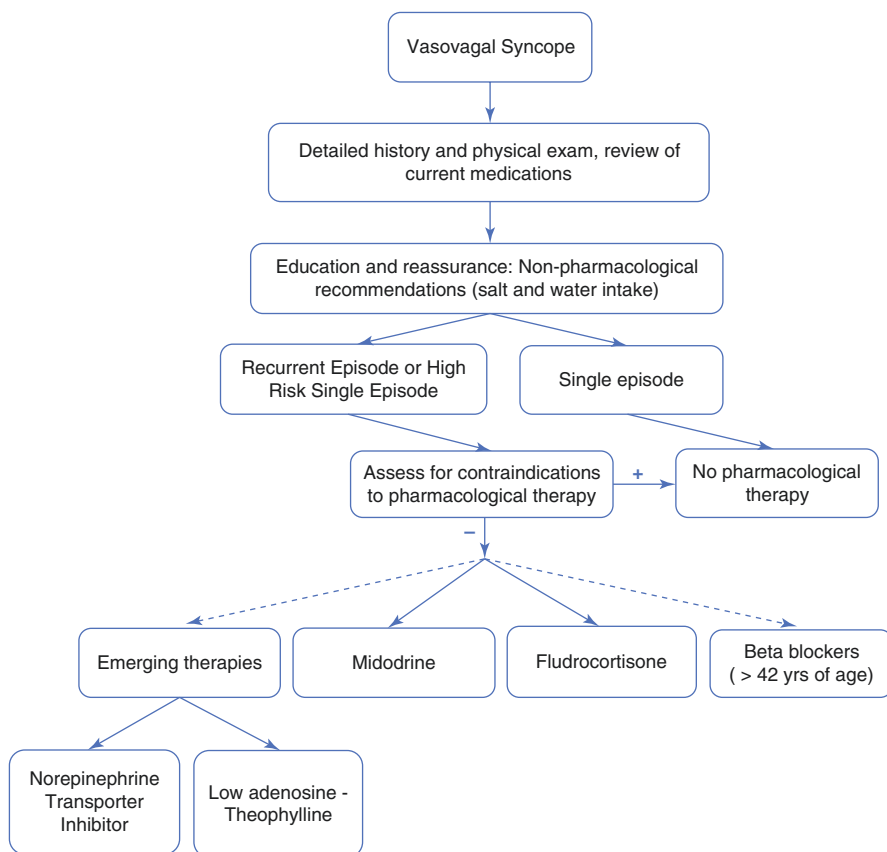


Fig. 23.1 A comprehensive algorithm for non-pharmacological and pharmacological treatment options in patients with vasovagal syncope (VVS), based on the recommendations of leading professional organizations (European Society of Cardiology, American Heart Association, American College of Cardiology, and Heart Rhythm Society). High risk features of VVS include lack of prodromes leading to trauma, disruption of work/school, personal suffering, and syncope while driving. Dash lines indicate unclear evidence with proposed regimens. Further studies investigating the effect of beta-blockers, norepinephrine transporter (NET) inhibitors, and theophylline will provide a more clear direction in treatment of patients with VVS

23.2 Discontinuation of Blood Pressure Lowering Medications in VVS

23.2.1 *The Guidelines Speak*

HRS 2015

- Reducing or withdrawing medications that can cause hypotension can be beneficial for patients with VVS (Class IIa) [3].

AHA/ACC/HRS 2017

- In selected patients with VVS, it may be reasonable to reduce or withdraw medications that cause hypotension when appropriate (Class IIb) [4].

ESC 2018

- Modification or discontinuation of hypotensive drug regimen should be considered in patients with vasodepressor syncope, if possible (Class IIa) [1].

23.2.2 Commentary

Patients with VVS, being treated for other co-morbidities should be carefully assessed for the vasodepressor effect of pharmacological therapies. Many agents, including antihypertensive, heart failure, antidepressants, and dopaminergic medications can reduce the vessel tones and promote the VVS [1]. By way of example, STOP-VD, a recently published small randomized trial showed that in patients with VVS, discontinuation of the vasodepressor agents leads to a lower incidence of the events in the treated arm versus the control arm of the study (23% vs. 54%, $P = 0.02$, HR 0.37 [95% CI 0.15 to 0.91]) [5]. Most patients in this small study were on antihypertensive agents; however, other vasodepressor agents were also adjusted or discontinued.

Optimizing vasodepressor agents in patients with proven hypertension or heart failure can be challenging in patients with VVS. Careful and iterative assessment of the pharmacological therapies, combined with slightly more liberal BP control that suggested by the blood pressure guidelines, may prove to be beneficial in patients with recurrent VVS.

23.3 Non-Pharmacological Therapies for VVS

23.3.1 Water and Salt Intake

23.3.1.1 The Guidelines Speak

HRS 2015

- Education, reassurance, and promoting salt and fluid intake are indicated for patients with VVS, unless contraindicated (Class I) [3].

AHA/ACC/HRS 2017

- Encouraging increased salt and fluid intake may be reasonable in selected patients with VVS, unless contraindicated (Class IIb) [4].

ESC 2018

- No clear recommendation by the panel. However, it has been mentioned as part of “explanation of the diagnosis, the provision of reassurance, and explanation of the risk of recurrence and the avoidance of triggers and situations are indicated in all patients” (Class I) [1].

23.3.1.2 Commentary

Many studies investigated the effect of fluid and salt intake in patients with VVS. In this context, EPISoDe study, a recently published randomized controlled trial investigated the effect of water bolus intake prior to blood donation. This study showed that the frequency of syncopal events was reduced by 23% in the treatment arm of the study (95% CI 6–37%) [6], regardless of the volume of water intake. This study is the largest trial studying the effect of water bolus intake in young adults.

In addition to water intake, another study investigated the effect of oral rehydration salts in children with known VVS. This study showed that syncopal frequency and positive head-up tilt testing were significantly reduced with oral rehydration salts and 500 ml of water compared to the placebo group ($P < 0.05$ and $P < 0.01$, respectively) [7]. However, it is unclear whether the results are due to the combination of oral rehydration salts and water, or if water intake alone would also have shown significant benefit.

A recent systematic review and meta-analysis showed that in the control groups of the observational and randomized trials, the relative risk of experiencing syncopal spells compared to prior year of enrollment is 0.44 (CI 95% 0.41–0.46). These data emphasize the effects of education, reassurance, and non-pharmacological measures in management of patients with VVS [8]. Currently, in addition to education and reassurance, increased water intake (targeting up to 3 L/day) and salt intake (targeting up to 8–10 g/day) is recommended in patients without specific contraindication to augmented water and salt intake. Patients for whom such recommendations might not be appropriate include those with hypertension, renal disease, and heart failure [4]. This approach to therapy requires a continuous risk/benefit analysis over time, as patient status can change over time.

Reassurance, education, and increased water and salt intake should be the cornerstones of therapy in young patients and patients without any contraindication to these measures.

23.3.2 Physical Counter-Pressure Maneuvers

23.3.2.1 The Guidelines Speak

HRS 2015

- Physical counter-pressure maneuvers can be useful for patients with VVS who have a sufficiently long prodromal period (Class IIa) [3].

AHA/ACC/HRS 2017

- Physical counter-pressure maneuvers can be useful in patients with VVS who have a sufficiently long prodromal period (Class IIa) [4].

ESC 2018

- Isometric physical counter-pressure maneuvers should be considered in patients with prodromes who are <60 years of age (Class IIa) [1].

23.3.2.2 Commentary

Physical counter-pressure maneuvers are important in management of patients with VVS, although they are more effective in patients with sufficiently prolonged prodromes to allow them to react. The PC-Trial showed a significant reduction in recurrence and total number of syncopal spells among VVS patients trained in counter-pressure maneuvers compared to untrained patients (31.6% vs. 50.9%; $P = 0.005$; relative risk reduction (RRR) = 0.39 [95% CI 0.11–0.53]) [9]. These maneuvers are low risk, low cost, and effective among patients who are able to perform the maneuvers. These maneuvers are less effective in patients with short or no prodromal symptoms, and among patients older than 60 years [10]. Older patients may become unstable with higher risk of falling during such maneuvers. VVS patients should be educated about how to perform these physical counter-pressure maneuvers.

23.4 Pharmacological Therapies for VVS**23.4.1 *Alpha-1 Agonists*****23.4.1.1 The Guidelines Speak**

HRS 2015

- The use of midodrine seems reasonable for patients with frequent VVS and no hypertension or urinary retention (Class IIb) [3].

AHA/ACC/HRS 2017

- Midodrine is reasonable in patients with recurrent VVS with no history of hypertension, HF, or urinary retention (Class IIa) [4].

ESC 2018

- Midodrine may be considered in patients with the orthostatic form of VVS (Class IIb) [1].

23.4.1.2 Commentary

Etilefrine and midodrine are both alpha-1 agonists (or prodrugs) which are used to engender vasoconstriction and venoconstriction, and to maintain vascular tone. Etilefrine was studied in a double-blinded randomized controlled trial (RCT), but

failed to show a reduction in burden of syncope [11]. Midodrine has been studied in a series of small studies, and showed promising results in 2011 Cochrane systemic review with respect to reducing the number of tilt table induced syncope, trauma secondary to syncope and quality of life [12]. However, the STAND trial, a small double-blinded crossover RCT published in 2011, failed to reproduce the findings of the prior studies [13]. More recently, Izcovich et al. [14] published a systematic review reviewing the efficacy of midodrine in patients with symptomatic orthostatic hypotension and recurrent reflex syncope. Meta-analysis data confirmed that midodrine is effective in improving quality of life, symptoms and syncope in recurrence compared to placebo. Commonly reported side effects included goosebumps, piloerector erection (hair standing on end), supine hypertension, and urinary retention [14]. The Fourth Prevention of Syncope Trial (POST4) will be the first adequately powered trial studying the efficacy of midodrine in prevention of syncope recurrence [15].

Currently, both European and American guidelines suggest that there is moderate degree of evidence for midodrine to be used as a therapy for patients with VVS who do not respond to conservative measures, and who do not have a relative contraindication such as heart failure, urinary retention, or supine hypertension. The need for frequent dosing, a lack of clear efficacy, and frequent side effects limit the use of midodrine as a front-line option for VVS treatment [4].

23.4.2 Fludrocortisone

23.4.2.1 The Guidelines Speak

HRS 2015

- The use of fludrocortisone seems reasonable for patients with frequent VVS who lack contraindications for its use (Class IIb) [3].

AHA/ACC/HRS 2017

- Fludrocortisone might be reasonable for patients with recurrent VVS and inadequate response to salt and fluid intake, unless contraindicated (Class IIb) [4].

ESC 2018

- Fludrocortisone may be considered in young patients with the orthostatic form of VVS, low-normal values of arterial BP, and the absence of contraindication to the drug (Class IIb) [1].

23.4.2.2 Commentary

Fludrocortisone increases the renal sodium absorption leading to increased salt and water retention, expanded blood volume, and subsequent higher venous return. Small pediatric studies suggested that fludrocortisone is beneficial in treatment of VVS [4].

The Second Prevention of Syncope Trial (POST2) [16] was the first randomized placebo-controlled trial studying the effect of fludrocortisone in prevention of VVS with the primary outcome goal of achieving a 40% RRR in frequency of syncope with treatment. The study was negative for the primary outcome. At 12 months, 56% of patients in the fludrocortisone group were syncope-free, compared to 39.5% of patients in the control group (31% RRR; $P = 0.07$). Post hoc analysis of POST2 showed a significant reduction in syncope recurrence if the 2-week dose stabilization period was censored from analysis (hazard ratio [HR]: 0.62; 95% CI: 0.40–0.95; $p = 0.029$), and among patients who reached the target dose of fludrocortisone 0.2 mg/day (HR: 0.51; 95% CI: 0.28–0.89; $P = 0.019$) [16].

Fludrocortisone, at a stable dose of 0.2 mg, could be considered in high risk patients, who experience frequent or have “high risk features” of syncope, in the absence of contraindications to fludrocortisone such as presence or development of hypokalemia, heart failure, peripheral edema, or hypertension.

23.4.3 *Beta-Blockers*

23.4.3.1 The Guidelines Speak

HRS 2015

- Beta-blockers may be considered for patients older than 40 years with frequent VVS (Class IIb) [3].

AHA/ACC/HRS 2017

- Beta-blockers might be reasonable in patients 42 years of age or older with recurrent VVS (Class IIb) [4].

ESC 2018

- Beta-adrenergic blocking drugs are not indicated (Class III) [1].

23.4.3.2 Commentary

Beta-blockers represent an area of divergence between European and American guidelines. Two randomized trials have investigated the effect of atenolol [11] and metoprolol [11] in patients with VVS, and each failed to show the benefit of beta-blockers. A 2011 Cochrane systematic review assessing the beta-blocker trials did not find any benefits in using beta-blocker therapy compared to placebo or other agents [12]. Sheldon et al. have published a subgroup analysis from the POST trial which showed a HR of 0.48 for metoprolol in patients ≥ 42 years, compared with a HR of 1.54 for metoprolol in patients < 42 years [11]. Based on these data, the ACC/AHA/HRS guidelines put beta-blockers as a class IIb recommendation, and indicate that it is reasonable to initiate therapy in patients ≥ 42 years. The POST5

placebo-controlled randomized trial is currently evaluating the efficacy of beta-blockers among patients with VVS who are >40 years [15]. Currently, we do not have sufficient data to prove that beta-blockers will be effective in older patients with VVS.

23.4.4 *Selective Serotonin Reuptake Inhibitors*

23.4.4.1 The Guidelines Speak

HRS 2015

- None

AHA/ACC/HRS 2017

- In patients with recurrent VVS, a selective serotonin reuptake inhibitor might be considered. (Class IIb) [4].

ESC 2018

- None

23.4.4.2 Commentary

There is very limited data studying the effect of paroxetine and fluoxetine in patients with VVS [1, 12]. When studies have compared SSRIs to placebo and beta-blockers, no clinical benefit has been observed [12]. Although there is an AHA/ACC/HRS class IIb indication for SSRI in patients with VVS, the level of evidence is based on limited data and poorly structured studies [4].

23.4.5 *Theophylline*

23.4.5.1 The Guidelines Don't Speak

23.4.5.2 Commentary

Recently, a new entity of syncope presentation has been identified. These patients experience sudden onset of syncope without any prodromes. Contrary to patients with typical VVS, these patients tend to have lower baseline plasma adenosine levels. These patients may have lower concentration of A2A receptors and experience a more severe degree of atrioventricular node block with adenosine exposure [17].

Theophylline, a non-selective adenosine receptor antagonist, has been shown to reduce the frequency of asystolic pauses and subsequent syncopal spells in patients with suspected “low adenosine syncope.” Currently, studies for low adenosine syncope are at very early stages. While measuring adenosine plasma concentrations may not be feasible in all centers [1], one should keep “low adenosine syncope” in the differential diagnosis of a patient with syncope, especially in the absence of a prodrome. We suggest expert consultation prior to initiation of therapy for suspected low adenosine syncope.

23.4.6 Norepinephrine Transport (NET) Inhibitors

23.4.6.1 The Guidelines Don’t Speak

23.4.6.2 Commentary

NET is a transporter on pre-synaptic sympathetic neurons that are important in the clearance of released norepinephrine from the synapse. NET inhibition results in increased sympathetic tone, and has been shown to reduce the frequency of tilt-induced syncope in healthy subjects [18] and clinical syncope in highly symptomatic patients who are refractory to other therapies [19]. The Sixth Prevention of Syncope Trial (POST6) [20] found that atomoxetine, a potent NET inhibitor marketed for attention deficit disorder, significantly reduced the number of tilt-induced syncope compared to placebo in patients with VVS (24% vs. 63%; $P = 0.003$ with logrank HR [95% CI: 0.18–0.87]). Atomoxetine seemed to do this largely by eliminating VASIS 2B (cardioinhibitory) reactions during tilt test.

NET inhibition provides exciting and promising results in treatment of patients with VVS. This is a novel mechanism of therapy for VVS. A proper randomized clinical trial with a primary endpoint of clinical syncope is required.

23.5 Conclusions

Despite multiple studies, the optimal management of VVS remains unclear. Currently, there is not a single proven therapy for patients with VVS. While VVS is often believed to be a benign condition, some patients with VVS can experience severe decline in their quality of life and experience physical trauma. Understanding the pathophysiology of syncope remains the potential key solution to develop future novel therapies. Ongoing randomized controlled trials investigating the effects of beta-blockers, alpha-1 agonists, and NET inhibitors may provide further insights into the management of patients with VVS.

Conflict of Interest Satish R Raj: None. Payam Pournazari: None.

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Chapter 24

Update on Cardiac Pacing in Reflex Syncope



Justin Z. Lee and Win-Kuang Shen

24.1 Introduction

Reflex syncope is defined as syncope due to a neural reflex mechanism that causes vasodilation, bradycardia, or both [1]. This is a broad category that includes vasovagal syncope, carotid sinus syndrome, situational faints, and other non-classical forms of reflex syncope such as low-adenosine syncope. The main rationale of cardiac pacing in patients with reflex syncope is that cardiac pacing may overcome the bradycardia and asystolic response from the cardioinhibitory reflex. However, cardiac pacing does not prevent the vasodepressor response of vasodilation and hypotension in reflex syncope (Fig. 24.1). The goal of this chapter is to discuss the role of pacing in the various subgroups of reflex syncope utilizing available studies and guidelines. Choice of pacing mode in reflex syncope and the role of diagnostic algorithm for decision on cardiac pacing will also be discussed.

24.2 Vasovagal Syncope

Vasovagal syncope is the most common form of reflex syncope. It is typically associated with symptoms of diaphoresis, warmth, nausea, and pallor, and is often followed by fatigue. Vasovagal syncope is often preceded by identifiable triggers and/or by a characteristic prodrome. There is an associated complex neural-cardiac

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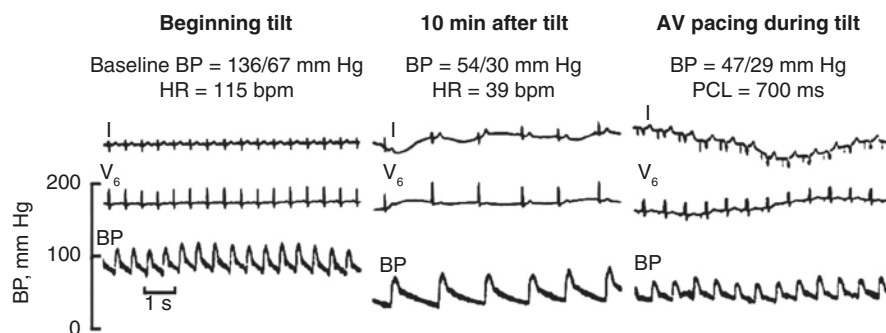


Fig. 24.1 Mixed cardioinhibitory and vasodepressor response during tilt-table testing. Electrocardiographic and arterial blood pressure recordings are shown. Left, Asymptomatic. Middle, During syncope. Heart rate and blood pressure decrease markedly. Patient experiences typical symptoms. Right, dual-chamber pacing with atrioventricular (AV) pacing cycle length (PCL) of 700 ms results in an increased heart rate, but the patient is still hypotensive and symptomatic. The results of this test suggest that the patient's symptoms are primarily due to the vasodepressor component, and they are unlikely to be relieved by permanent pacing. (Neurocardiogenic syncope: latest pharmacological therapies. Lin Y Chen and Win-Kuang Shen. Expert Opinion on Pharmacotherapy, 30 May 2006. Reprinted by permission of the publisher Taylor & Francis Ltd., <http://www.tandfonline.com>)

reflex that may manifest as bradycardia and/or hypotension. Most episodes of vasovagal syncope are self-limiting. However, in some patients, vasovagal syncope can be recurrent despite multiple non-pharmacological or pharmacological approaches. Therefore, cardiac pacing has been postulated to be effective via prevention of severe bradycardia and asystole during the vasovagal episode (Fig. 24.2).

24.2.1 Studies on Pacing in Vasovagal Syncope

There have been multiple randomized trials that assessed the role of pacing in patients with vasovagal syncope (Table 24.1). The Vasovagal Pacemaker Study (VPS I) included patients with recurrent syncope and a tilt test that induced both syncope or presyncope and relative bradycardia [2]. These patients were randomized to dual-chamber pacing versus no pacemaker. Syncope recurrence was reduced in patients with a pacemaker compared to patients without a pacemaker (22% vs. 70%, $p < 0.001$). However, a placebo effect accompanying cardiac pacing could not be excluded as the study was not blinded.

The Vasovagal Syncope International Study (VASIS) also showed benefit in favor of pacing [3]. The study included patients with recurrent syncope over two years and a positive cardioinhibitory response during tilt-table testing. Similar to the VPS I study, patients were randomized to dual-chamber pacing versus no pacemaker. At around 7 years, recurrence of syncope in the pacemaker group was only 5%. This was much lower compared to the recurrence rate of 61% in the

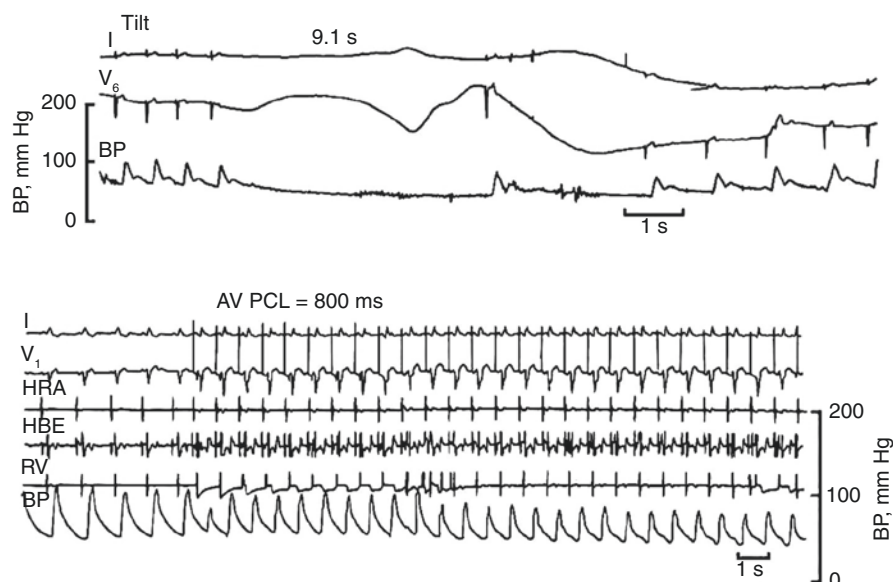


Fig. 24.2 Top panel, Significant cardioinhibitory response during tilt-table testing. There is a prolonged pause due to sinus arrest with significant hypotension. Lower panel, Absence of significant hypotension when bradycardia is prevented by pacing. Electrocardiographic and arterial blood pressure recordings are shown. (Neurocardiogenic syncope: latest pharmacological therapies. Lin Y Chen & Win-Kuang Shen. Expert Opinion on Pharmacotherapy, 30 May 2006. Reprinted by permission of the publisher Taylor & Francis Ltd., <http://www.tandfonline.com>). AV indicates atrioventricular; BP, blood pressure; HBE, His bundle electrogram; HRA, high right atrial electrogram; PCL, pacing cycle length; RV, right ventricular electrogram

group that did not receive a pacemaker. However, similar to the VPS I, a placebo effect could not be ruled out.

The Syncope Diagnosis and Treatment (SYDIT) study also showed benefit in favor of pacing and also could not exclude a placebo response to pacing [4]. Patients with recurrent syncope and tilt-table testing with syncope occurring in association with relative bradycardia (<60 bpm) were randomized to dual-chamber pacing versus atenolol. In patients who received a pacemaker, there was a lower syncope recurrence of 4.3% after a median follow-up of 390 days compared to the 25.5% in the atenolol group after a median follow-up of 135 days ($p = 0.004$).

The VPS I, VASIS, and SYDIT studies were limited by the absence of a placebo group. To determine the impact of a placebo response, the VPS II and the SYNPACE (Vasovagal Syncope and Pacing Trial) studies were performed [5, 6]. In both studies, the patients in the control group also underwent pacemaker implantation and had their pacemakers turned to sensing only (ODO) or off (OOO). However, both studies did not find benefit from pacing. This indicated a potential contributory placebo effect of cardiac pacing in patients with vasovagal syncope. However, both VPS II and SYNPACE enrolled patients without an asystolic tilt response and intense bradycardia was not an entry criterion.

Table 24.1 Randomized trials of pacing therapy in vasovagal syncope, pacing therapy in carotid sinus syndrome, and closed-loop stimulation for vasovagal syncope

Author, Year	Study aim	Endpoint	Intervention (event rate)	Comparator (event rate)	<i>P</i> -value
<i>Pacing therapy in vasovagal syncope</i>					
Flammang [17]	Pacing therapy in patients with VVS and abnormal cardioinhibitory response during ATP test	Syncope recurrence at 52 months	Pacemaker (0%)	No pacemaker (60%)	<0.02
Connolly (VPS) [2]	Pacing in VVS with tilt test that induced syncope or presyncope, as well as relative bradycardia	Syncope recurrence	Pacemaker (22%)	No pacemaker (70%)	<0.0001
Sutton (VASIS) [3]	Pacing therapy in cardioinhibitory tilt positive VVS	Syncope recurrence at 80 months	Pacemaker (5%)	No pacemaker (61%)	0.0006
Ammirati (SYDIT) [4]	Pacing in VVS positive tilt-table testing with syncope occurring in association with relative bradycardia (<60 bpm)	Syncope recurrence at 135 to 390 days	Pacemaker (4.3%)	Beta-blockers (25.5%)	0.004
Connolly (VPS II) [5]	Pacing therapy in VVS	Syncope recurrence at 6 months	Pacing DDD (33%)	PACING ODO (42%)	NS
Raviele et al. (SYNPACE) [6]	Pacing therapy in VVS with positive tilt test with asystolic or mixed response	Syncope recurrence at 24 months	Pacemaker ON (50%)	Pacemaker OFF (38%)	0.58
Brignole (ISSUE-3) [18]	Pacing therapy in asystolic neurally mediated syncope	Syncope recurrence at 24 months	Pacemaker ON (21.1%)	Pacemaker OFF (48.7%)	0.039
<i>Pacing therapy in carotid sinus syndrome</i>					
Brignole [11]	Pacing therapy in CI-CSS	Recurrent syncope at 36 months	Pacemaker (9%)	No pacemaker (57%)	0.0002
Kenny (SAFE PACE) [19]	Pacing therapy in reduction of falls in older patients with CI-CSH	Recurrent syncope at 12 months	Pacemaker (11%)	No pacemaker (22%)	0.063
Claesson [12]	Pacing therapy in CI-CSS	Recurrent syncope at 12 months	Pacemaker (10%)	No pacemaker (40%)	0.008

Table 24.1 (continued)

Author, Year	Study aim	Endpoint	Intervention (event rate)	Comparator (event rate)	<i>P</i> -value
Parry [20]	Pacing therapy in patients with CI-CSH and recurrent falls	Number of falls	Pacemaker in DDD/RDR (4.04 falls)	Pacemaker in ODO (3.48 falls)	NS
Ryan (SAFE PACE 2) [21]	Pacing therapy in older patients with CI-CSH and unexplained falls	Syncope recurrent events at 24 months	Pacemaker (0.42 mean events)	No pacemaker (0.66 mean events)	–
<i>Closed-loop stimulation for cardioinhibitory vasovagal syncope*</i>					
Occhetta (INVASYS) [22]	Effect of dual-chamber CLS in patients with CI-VVS	Syncope recurrence at 12 months	DDD-CLS (0%)	DDI (78%)	–
Russo [23]	Effect of dual-chamber CLS in syncope recurrence in patients with cardioinhibitory VVS	Syncope recurrence at 18 months	CLS programmed on (2%)	CLS programmed off (16%)	0.007
Baron-Esquivias (SPAIN) [14]	Pacing with DDD-CLS in patients with CI-VVS	≥50% reduction in syncope recurrence	DDD-CLS (72%)	Sham DDI (28%)	–
Palmisano (TIRECS) [15]	Effect of CLS pacing in syncope induced by tilt test in patients with CI-VVS	Syncope during tilt test	DDD-CLS (30%)	DDD (76.7%)	<0.001

ATP adenosine triphosphate, CI cardioinhibitory, CLS closed-loop stimulation, CSH carotid sinus hypersensitivity, CSS carotid sinus syndrome; NS not significant, VVS vasovagal syncope

*The BIOSync CLS study has been completed but is not yet published

These issues prompted the development of the International Study on Syncope of Uncertain Etiology 2 (ISSUE-2) registry which suggested that there may be a role for pacing in patients with VVS with documented cardio-inhibition on implantable loop recorder (ILR) [7]. This finding was confirmed in the Third International Study on Syncope of Uncertain Etiology (ISSUE-3) trial. ISSUE-3 was a double-blinded, randomized, placebo-controlled study which included patients ≥40 years old with three or more syncopal episodes of likely reflex etiology (carotid sinus syndrome was excluded) in the preceding 2 years who had documentation of asystole (≥3 s with a symptomatic episode, or ≥6 s without symptoms) on implantable loop recorder. All patients received a pacemaker and were randomized to pacemaker on DDD pacing with rate-drop response versus sensing only. Syncope recurrence was lower in the pacing group compared to the placebo group (21% vs. 49%, $p = 0.039$).

A substudy of the ISSUE-3 showed that patients with the most benefit from cardiac pacing were patients with a negative tilt study with ILR documented asystolic episodes, suggesting that a positive tilt study identifies patients with a dominant vasodepressive mechanism of syncope whereas patients with a negative tilt study with ILR documented asystolic episodes have a more dominant cardioinhibitory mechanism for their syncope [8].

24.2.2 Guideline Recommendations for Pacing in Vasovagal Syncope

The 2017 ACC/AHA/HRS syncope guideline recommends that dual-chamber pacing might be reasonable in a select population of patients 40 years of age or older with recurrent vasovagal syncope and prolonged spontaneous pauses (Table 24.2) [1]. The 2018 ESC syncope guidelines recommend that cardiac pacing should be considered to reduce syncope recurrences in patients aged >40 years, with spontaneous documented symptomatic asystolic pause(s) >3 s or asymptomatic pause(s) >6 s due to sinus arrest, AV block, or a combination of the two [9]. The ESC recommended that cardiac pacing may be considered to reduce syncope recurrences in patients with tilt-induced asystolic response who are >40 years with recurrent frequent unpredictable syncope [9]. Furthermore, ESC also recommends that cardiac pacing is not indicated if there is no documented cardioinhibitory reflex.

The ACC/AHA/HRS provided a single Class IIb recommendation for pacing in reflex syncope, whereas the ESC guidelines provided three separate recommendations (Class IIa, IIb, and III) on pacing in reflex syncope. The difference in both guidelines is likely due to a different methodology for evidence review and also different writing policies. In the ACC/AHA/HRS syncope guideline, a separately commissioned systematic review of the literature was performed by an Evidence Review Committee that utilized the PICOT framework (population, intervention, comparison, outcome, and timing) [10]. With the one specific PICOT question on the effectiveness of pacing in patients with reflex-mediated syncope, the aggregate evidence supported an overall Class IIb recommendation for pacing in selected patients with reflex syncope in the ACC/AHA/HRS guideline. With a different

Table 24.2 Guideline recommendations on pacing therapy in vasovagal syncope

Guideline	Class ^a	Level ^b
<i>Recommendations of the 2017 ACC/AHA/HRS syncope guideline</i>		
Dual-chamber pacing might be reasonable in a select population of patients ≥40 years of age with recurrent vasovagal syncope and prolonged spontaneous pauses	IIb	B
<i>Recommendations of the 2018 ESC guidelines of the diagnosis and management of syncope</i>		
Cardiac pacing should be considered to reduce syncope recurrences in patients aged >40 years, with spontaneous documented symptomatic asystolic pause(s) >3 s or asymptomatic pause(s) >6 s due to sinus arrest, atrioventricular block, or a combination of the two	IIa	B
Cardiac pacing may be considered to reduce syncope recurrences in patients with tilt-induced asystolic response who are >40 years with recurrent frequent unpredictable syncope	IIb	B
Cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex	III	B

^aClass of recommendation

^bLevel of evidence

methodology and guideline writing policy, the ESC guidelines provided three recommendations, each with its own class of recommendation, that addressed different patient groups with reflex syncope.

24.3 Carotid Sinus Syndrome

Reflex syncope can also be associated with carotid sinus hypersensitivity. Carotid sinus syndrome is diagnosed when there is a reproduction of spontaneous symptoms associated with a cardioinhibitory response (pause ≥ 3 s) and/or vasodepressor component (decrease of systolic pressure ≥ 50 mm Hg) upon stimulation of the carotid sinus.

24.3.1 *Studies on Pacing in Carotid Sinus Syndrome*

The role of cardiac pacing in patients with carotid sinus syndrome has been studied in a few small randomized trials (Table 24.1). In 1992, Brignole et al. showed in a randomized trial of cardiac pacing in patients with cardioinhibitory carotid sinus syndrome that pacemaker reduced recurrence of syncope at 3 years compared to no pacemaker (9% vs. 57%, $p = 0.0002$) [11]. In 2007, Claesson et al. showed that in 60 patients with cardioinhibitory CSS, there was a lower rate of recurrent syncope at 1 year in patients who received a pacemaker compared to no pacemaker (10% vs. 40%, $p = 0.008$) [12].

24.3.2 *Guideline Recommendations for Pacing in Carotid Sinus Syndrome*

The 2017 ACC/AHA/HRS syncope guideline recommends that permanent cardiac pacing is reasonable in patients with carotid sinus syndrome that is cardioinhibitory or mixed (Table 24.3) [1]. It may also be reasonable to implant a dual-chamber pacemaker in patients with carotid sinus syndrome who require permanent pacing. The 2018 ESC syncope guideline recommends that cardiac pacing should be considered to reduce syncope recurrence in patients with cardioinhibitory carotid sinus syndrome who are >40 years with recurrent frequent unpredictable syncope [9]. As there are similar outcomes of patients with reflex spontaneous asystolic pauses and those with carotid sinus syndrome, the ESC Task Force downgraded (from the 2009 iteration of the syncope guideline) the recommendation for pacing in patients with carotid sinus syndrome from Class I to Class IIa.

Table 24.3 Guideline recommendations on pacing in carotid sinus syndrome

	Class ^a	Level ^b
<i>Recommendations of the 2017 ACC/AHA/HRS syncope guideline</i>		
Permanent cardiac pacing is reasonable in patients with carotid sinus syndrome that is cardioinhibitory or mixed	IIa	B
It may be reasonable to implant a dual-chamber pacemaker in patients with carotid sinus syndrome who require permanent pacing.	IIb	B
<i>Recommendations of the 2018 ESC guidelines of the diagnosis and management of syncope</i>		
Cardiac pacing should be considered to reduce syncope recurrence in patients with cardioinhibitory carotid sinus syndrome who are >40 years with recurrent frequent unpredictable syncope	IIa	B

^aClass of recommendation

^bLevel of evidence

24.4 Low-Adenosine Syncope

Adenosine and its receptors have been proposed to be involved as a modulator in triggering reflex response in some patients. Low-adenosine syncope has been described in patients with sudden onset unexplained syncope without prodrome, a normal heart with no features of conduction disease on ECG, low plasma adenosine levels, and a high induction rate of transient complete heart block with exogenous injections of adenosine [9]. In the ATP multicenter study of elderly patients with unexplained syncope and positive ATP tests, dual-chamber pacing reduced syncope recurrence by 75% (95% CI 44–88) [13]. A positive ATP test was defined as sinoatrial block lasting for more than 10 s under a 20-mg intravenous bolus of ATP. The ESC guideline for syncope recommends that cardiac pacing may be considered to reduce syncope recurrences in patients with clinical features of adenosine-sensitive syncope (Class of Recommendation IIb, Level of Evidence B) [9]. In the ACC/AHA/HRS guideline for syncope, there is no recommendation on the use of adenosine triphosphate in the evaluation for syncope because of limited data.

24.5 Choice of Pacing Mode

Dual-chamber pacing is widely preferred in clinical practice compared to single-chamber pacing for reflex syncope. In carotid sinus syndrome, there are a few small controlled studies that showed dual-chamber pacing to be better than single-chamber pacing in counteracting the blood pressure fall during carotid sinus massage and in preventing symptom recurrences [9, 10].

Rate-drop response is the most commonly studied algorithm for vasovagal syncope. The main goal of the algorithm is to detect falls in heart rate and provide DDI or DDD pacing at an elevated rate for a limited time. Ideally, it should also attempt to ignore very gradual heart rate falls that occur naturally with relaxation or onset of

sleep. One of the limitations of the algorithm is that it can only sense impending vasovagal syncope by detecting a fall in the heart rate, which may be too late for effective introduction of pacing.

Therefore, the use of another sensed parameter in the setting of impending vasovagal syncope that is able to permit earlier triggering of pacing may be more effective. In vasovagal syncope, it has been suggested that an increase in cardiac contractility occurs when vasovagal syncope is imminent. Right ventricular cardiac contractility can be measured using intracardiac impedance as a surrogate. Closed-loop stimulation utilizes intracardiac impedance to increase pacing rate early during an episode of vasovagal syncope. Recently, there is increasing evidence that closed-loop stimulation (CLS) leads to fewer syncope recurrences compared to conventional dual-chamber pacing (Table 24.1).

The Closed Loop Stimulation for Neuromediated Syncope (SPAIN) study included patients who are ≥ 40 years old, recurrent syncope, and a positive cardio-inhibitory tilt study (bradycardia < 40 beats/min for 10 s or asystole > 3 s) [14]. The study results showed that there was a significantly greater reduction in syncope recurrence in patients who received cardiac pacing with DDD-CLS (72% of patients had $\geq 50\%$ reduction of syncope) compared with patients with sham DDI (28% of patients had $\geq 50\%$ reduction of syncope). In the Tilt test-Induced REsponse in Closed-loop Stimulation (TIRECS) study, the addition of closed-loop stimulation was shown to reduce the occurrence of syncope induced by tilt-table test compared to standard dual-chamber pacing and sensing, with both triggered and inhibited mode (DDD) (30% vs. 77%, $p < 0.001$) [15]. The BIOSync CLS multicenter randomized controlled study is likely to be published in late 2020, and will add to understanding of the utility of the CLS algorithm (Biotronik Inc, Berlin, Germany).

24.6 Diagnostic Algorithm for Decision on Cardiac Pacing in Reflex Syncope

Although cardiac pacing may be effective, it should only be considered in highly selected patients. One proposed algorithm was studied in the Syncope Unit Project 2 (SUP-2) study [16]. The study included patients aged > 40 years (mean age of 70 years) with severe (impaired quality of life), unpredictable (without or with very short prodromes), and recurrent (at least two episodes) reflex syncope. These patients underwent a comprehensive diagnostic algorithm, starting with carotid sinus massage to diagnose cardioinhibitory carotid sinus syndrome whereby dual-chamber pacemaker would be proposed. If carotid sinus massage was negative or the response was vasodepressor, patients underwent tilt testing. If the response was cardioinhibitory, a dual-chamber pacemaker was proposed. If the tilt study was negative or the response was vasodepressor, patients underwent implantable loop recorder implantation to detect any asystole episodes that would meet pacemaker criteria. With the standardized algorithm, the recurrence rate of syncope was reduced to 9% (95% CI, 6–12) at the first year, 15% (95% CI, 10–20) at the second year, and 20% (95% CI, 29–57) in the third year. These were lower than in

un-paced controls who had a recurrence rate of syncope of 22% (95% CI, 18–26) in the first year, 37% (95% CI, 30–43) in the second year, and 43% (95% CI, 29–57) in the third year.

Beyond algorithms for decision on cardiac pacing, the shared-decision making process is also important. This is especially critical in younger patients with recurrent vasovagal syncope despite conservative therapy and documented prolonged pauses. There is still insufficient data in this area. The short- and long-term risk of pacemaker implantation will need to be weighed against the beneficial effects of a pacemaker in this population.

24.7 Future Direction

Despite the data that is currently available, there are still several knowledge gaps that present opportunities for future research. One question is, how can we better identify a subgroup of patients that will benefit from pacing the most? Further investigations are also needed in closed-loop stimulation. With advances in pacemaker technology, is leadless pacemaker a reasonable strategy to reduce long-term pacemaker related complications? If so, how is its efficacy as a single-chamber device for reflex syncope before the clinical approval of the leadless dual-chamber pacemaker? Future technology such as rechargeable generators will likely reduce complications associated with generator replacement due to battery depletion. Will physiologic pacing such as His Bundle pacing be more effective than the conventional pacing from the right ventricular apex in this patient population?

24.8 Summary and Key Points

While most patients with reflex syncope can be managed with conservative therapy without the need for invasive interventions, select patients may benefit from cardiac pacing to reduce recurrent syncope. Cardiac pacing can be considered in recurrent vasovagal syncope for patients who are ≥ 40 years with features of cardioinhibitory reflex. Cardiac pacing can also be considered in cardioinhibitory carotid sinus syndrome. Cardiac pacing should not be offered to patients with reflex syncope without any evidence of cardioinhibitory reflex. There is increasing data on closed-loop stimulation (CLS) for vasovagal syncope and the use of diagnostic algorithms for facilitating decision-making on implantation of pacemaker in recurrent reflex syncope.

Disclosures Authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Chapter 25

Ictal Asystole: Relation to Reflex Syncope and Role of Cardiac Pacing



Haruhiko Abe and Ritsuko Kohno

25.1 Introduction

Syncope is a form of transient loss of consciousness (TLOC) which is self-limited and abrupt in onset and of short duration followed by spontaneous recovery. In young adults, syncope is most often due to vasovagal or autonomic reflex mechanisms, whereas in older patients, cardiac arrhythmias are often implicated. Seizures are also an important consideration in the differential diagnosis of patients who present with TLOC.

Most often the heart rate during a seizure demonstrates sinus tachycardia [1–3] associated with increase in sympathetic activity (ictal tachycardia). However, on rare occasions an apparent syncope may be due to seizure-induced asystole, a circumstance usually termed “ictal asystole.”

Seizure-related asystole includes both ictal and post-ictal asystole. “Post-ictal asystole” is rare, and observed after a focal seizure evolving into a bilateral convulsive seizure, in which case it was preceded by post-ictal generalized electroencephalogram (EEG) suppression. The precise pathophysiological mechanisms of post-ictal-related asystole are not established yet.

“Ictal asystole” occurs most often in patients with temporal lobe epilepsy. The mechanisms are still unclear, but increased parasympathetic activity directly or indirectly induced by the seizure may play a role. Most episodes of ictal asystole occur during the course of a focal dyscognitive seizure, starting approximately 30 seconds after seizure onset. The mean duration of ictal asystole is 20 s (range 3–96 s). The seizure shows temporal lobe abnormal activity in 90% cases without consistent lateralization [1].

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In order to deliver optimum treatment for ictal asystole, an accurate diagnosis must be made; this often entails using simultaneous long-term video EEG-ECG monitoring. A long-term subcutaneous implantable cardiac monitor (ICM) has also been useful in selected cases. The problem is a lack of awareness among non-neurologists including cardiologists and electrophysiologists regarding this phenomenon.

25.2 Asystolic Reflex Syncope

Reflex syncope occurs due to neural reflex responses with transient hypotension and diminished cerebral perfusion. The most common cause of reflex syncope is a vasovagal attack, which in the clinical laboratory may be induced by head-up tilt testing.

In general, the hemodynamics of reflex syncope comprises two components (vasodepressor and cardioinhibitory mechanisms). Either component can cause syncope, but most cases occur in response to a combination of both components (i.e., “mixed” form). The cardioinhibitory mechanism is mediated primarily through an increase in vagal tone, and it results in abrupt prolonged asystole or marked bradycardia. If asystole is sustained for a sufficiently long duration of time (usually more than 6 s after the last heart beat), the resulting cerebral hypoperfusion causes syncope [2]. Since relationships between strength and timing of vasodepressor and cardioinhibitory components exist in reflex syncope, different patterns of cerebral hypoperfusion may be observed [3].

In the selection of treatment options for recurrent vasovagal syncope, current US and Japanese clinical practice guidelines place are conservative with regard to pacing; listing it as Class IIb (Level of Evidence B-R). The ESC guidelines recommend pacing as a Class IIa recommendation in cardioinhibitory vasovagal syncope with documented symptomatic asystole for >3 s or asymptomatic asystole for >6 s [4–6]. These indications for cardiac pacing are based on the results of ISSUE 3 study (Third International Study on Syncope of Uncertain Etiology 3) [5]. In vasovagal syncope patients with a positive tilt table test, the recurrence rate after pacing therapy was very high at 55% over 21 months follow-up. On the other hand, in patients with a negative tilt test (i.e., neither cardioinhibitory or vasodepressor features evident), the recurrence rate of syncope after pacing therapy was very low at 5% [7]. ISSUE 3 results suggested that head-up tilt testing outcome can help predict the usefulness of pacing therapy in vasovagal patients with documented spontaneous prolonged asystole. It is, therefore, very important to perform head-up tilt testing before implantation of permanent pacemaker in suspected vasovagal syncope patients who have had documented prolonged asystole and are being considered for treatment with cardiac pacing.

25.3 Asystole in Patients with Temporal Lobe Epilepsy

There has been a long-recognized association between epilepsy and autonomic cardiovascular control, especially brady-arrhythmias. Ictal asystole has an incidence of 0.22–0.4% in monitored epilepsy patients, although the possibility of under-detection has to be taken into consideration; a recent study reported an incidence of ictal asystole of 16% of patients with refractory epilepsy using ICM [8]. The majority of previously reported cases of ictal asystole were observed in patients with temporal lobe epilepsy.

25.4 Pathophysiology of Ictal Asystole

The pathophysiological mechanism of ictal asystole is thought to be vagal-induced transient cardiac asystole leading to transient cerebral hypoperfusion. Two possible mechanisms play a part in ictal asystole or bradycardia (Fig. 25.1). The first involves induction of asystole due to the propagation of ictal activity from the temporal region to the adjacent insular lobe where a cardioinhibitory effect can be initiated [9]. One previous report suggested that experimental stimulation of the left insular cortex in patients with temporal epilepsy resulted in bradycardia independent of seizures, while

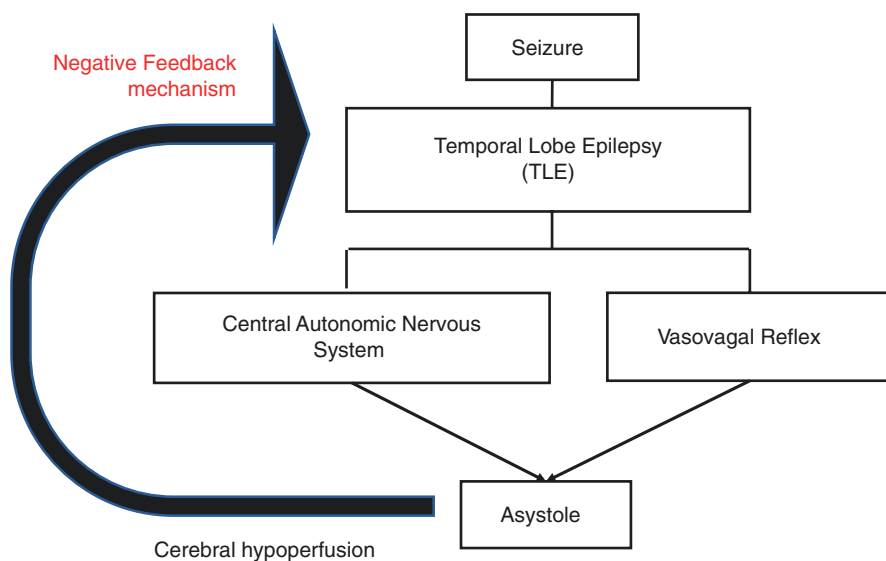


Fig. 25.1 Schema of the mechanisms for ictal asystole and negative-feedback mechanism. Ictal asystole is strongly associated with temporal lobe epileptic seizures. It could be a direct consequence of epileptic activity stimulating the central autonomic nervous system or an indirect effect of the seizure evoking a vasovagal reflex. Ictal asystole is self-limiting, as cerebral hypoperfusion and anoxia caused by the asystole terminate the epileptic seizure (negative-feedback mechanism). Figure is modified from reference [1].

stimulation of the right insular cortex induced tachycardia [10]. However, it is unclear whether this abnormal electrical activity was comparable to a spontaneous event ultimately propagated to the insula. Importantly, the ictal onset in all patients precedes the changes in the heart rate. The second possible mechanism of the pathophysiology suggests that epileptic activity affects the heart rate directly through an increase in vagal tone. It has been postulated that the vagus nerve located in the autonomic reflex centers of the brainstem may be stimulated by the spread of seizure activity. Such ictal autonomic dysfunction was proposed to independently cause cerebral hypoperfusion in addition to bradycardia or asystole. In light of this theory, the treatment of ictal asystole with a cardiac pacemaker might be proposed to reduce falls, fractures, and injuries. On the other hand, death is an unlikely consequence; direct evidence of a causative link between bradycardia and SUDEP is currently lacking.

Although the role of ictal asystole during a seizure has been obscure, a negative-feedback mechanism has been recently postulated (Fig. 25.1). This hypothesis proposes a negative-feedback mechanism in which temporal lobe epilepsy stimulates the central origins of the autonomic nervous system, especially those of the parasympathetic supply. Asystole reduces global cerebral blood flow and results in the termination of the epileptic seizure [1]. In fact, it has been reported that the total seizure duration is shorter for seizures with ictal asystole compared to those without [1, 11].

25.5 ECG Findings in Cardioinhibitory Vasovagal Syncope and Ictal Asystole

It is well known that ECG findings, especially in terms of heart rate changes, show very similar patterns in patients with vasovagal syncope as in those with ictal asystole. The similarity of heart rate changes might suggest that the same mechanisms are involved (i.e., increase in parasympathetic activity). As in emotionally induced vasovagal syncope, seizure may induce fear and catecholamine release, the result in both cases may culminate in cardioinhibition and vasodilatation.

Heart rate patterns preceding asystole are similar between subjects with ictal asystole and those with vasovagal syncope: heart rate increases markedly, followed by a progressive bradycardia, culminating in asystole. Vasovagal syncope is a self-limiting condition with an excellent long-term prognosis. Prolonged cerebral hypoperfusion is thought to shut down the initial central trigger, thereby explaining its benign course. Similarly, cerebral anoxia-ischemia in ictal asystole could be a potential mechanism of seizure self-termination as well.

A typical case of a 66-year-old man, whose ECG was recorded with an implantable loop recorder (ILR), is shown in Fig. 25.2. The patient showed bifascicular block on the ECG and recurrent syncope with prodromal symptoms followed by loss of consciousness. Since arrhythmic syncope was suspected, the patient was followed with an implantable loop recorder (ILR). The ILR recording shows a transient increase in heart rate followed by a gradual decrease and then the asystolic event (maximum 18 s asystole in this patient) occurred. The patient was diagnosed with temporal lobe epilepsy by electroencephalogram (EEG) associated with ictal asystole (Fig. 25.3). He was treated with an anti-epileptic drug (carbamazepine)

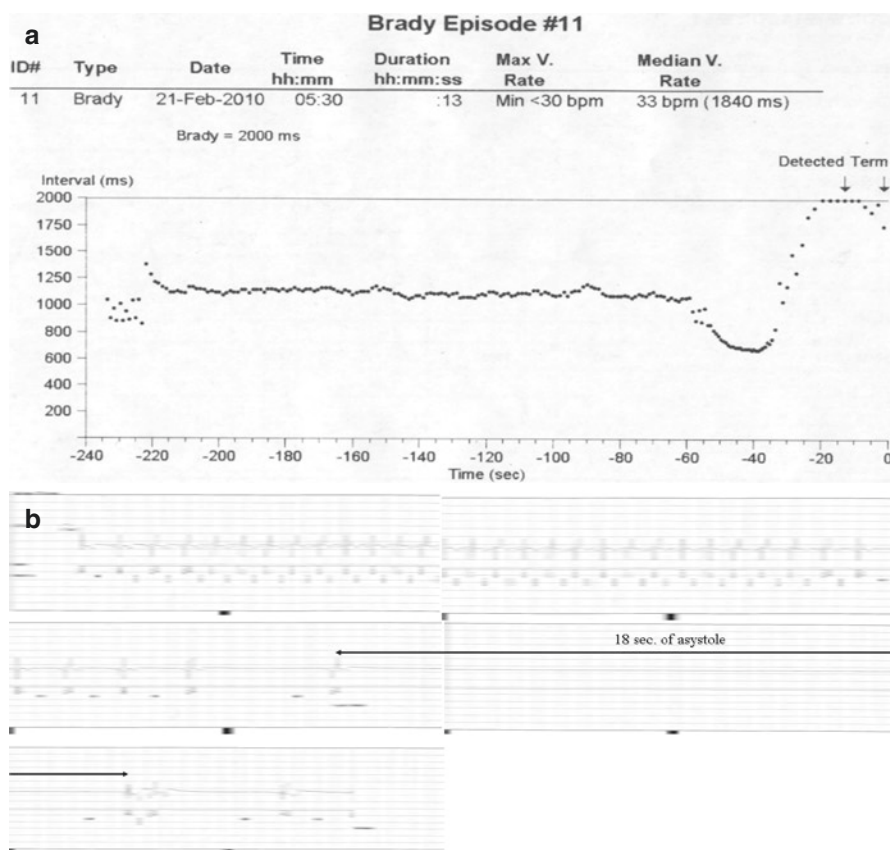


Fig. 25.2 Asystole, maximum duration of 18 s, is detected with an implantable loop recorder (ILR) in a 66-year-old man. **(a)** Heart rate trendgram shows transient increase heart rate followed by gradual decrease, and then development of an asystolic pause of 18 s. **(b)** ECG on ILR is shown

alone without cardiac pacing. Ictal asystole, syncope, and epileptic seizure disappeared completely after the treatment with carbamazepine alone, and he had no further asystolic events with ILR during 1.8 years of follow-up (Fig. 25.4) [12].

25.6 Role of Cardiac Pacing for Ictal Asystole

The usefulness of cardiac pacing therapy for ictal asystole has not been established to date. The dearth of guidelines and objective information stems from a lack of concomitant blood pressure data. Since ECG findings are similar in both ictal asystole and vasovagal asystole, the mechanism of ictal asystole is also presumed to be comparable to that for vasovagal syncope as discussed above. However, the role of the vasodepressor component in ictal asystole is less clear. Accordingly, based on current knowledge, cardiac pacing may therefore be useful to prevent collapse and injuries due to syncope if the seizure-related ictal asystole is primarily

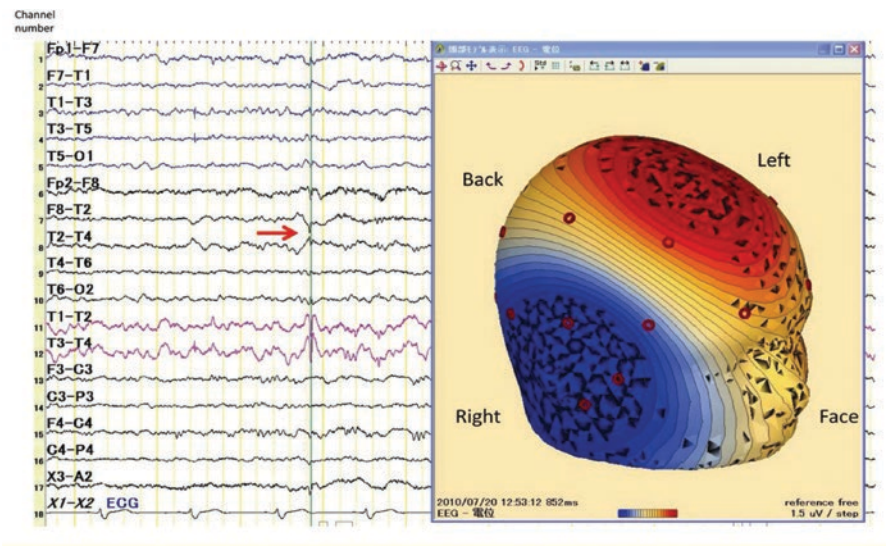


Fig. 25.3 The patient was diagnosed with temporal lobe epilepsy by electroencephalogram (EEG). Figure is adapted with permission from reference [12]

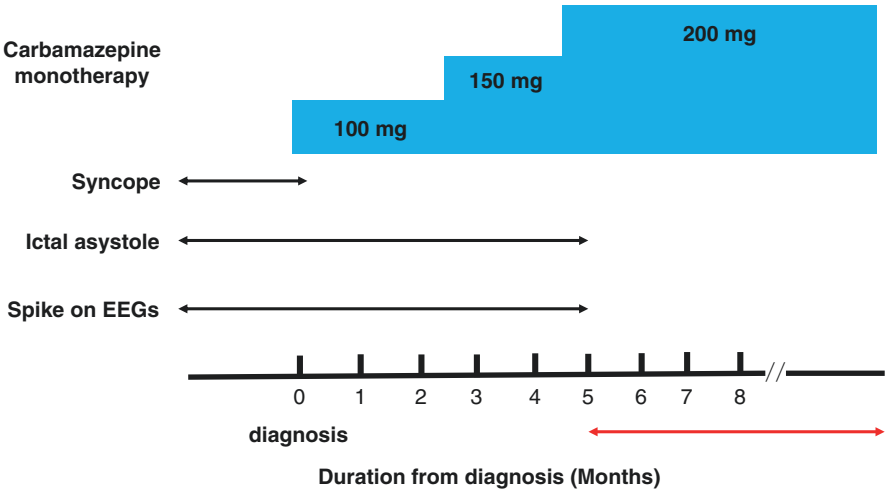


Fig. 25.4 Clinical course in this patient is shown. Syncopal symptom disappeared immediately following carbamazepine therapy. Since ictal asystole or bradycardia on ILR and spikes on EEG remained after carbamazepine at a dose of 100 mg/day, dose of carbamazepine was increased to 200 mg/day. Ictal asystole on ILR and spikes on EEG findings disappeared completely thereafter

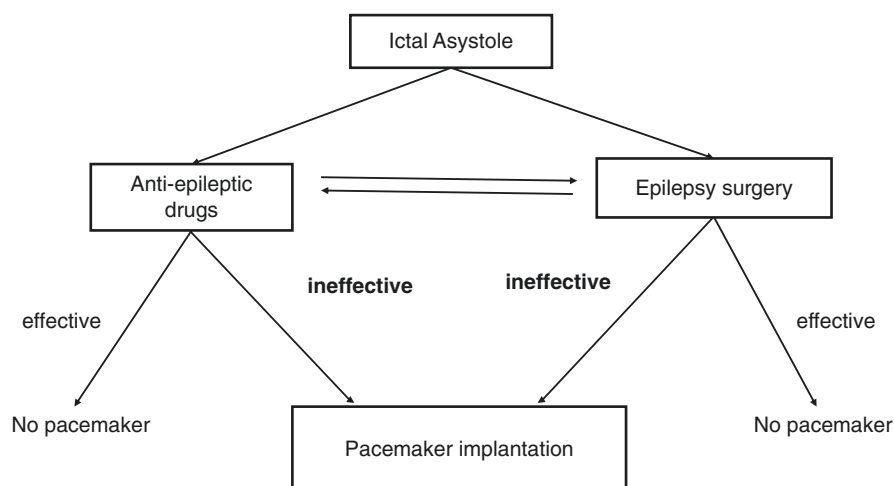


Fig. 25.5 Flowchart of therapeutic management of ictal asystole

cardioinhibitory in etiology. In addition, since cardiac pacing for ictal asystole may maintain or restore cerebral perfusion during an epileptic seizure, there is a possibility that there may be seizure prolongation with cardiac pacing [13, 14].

Recent publications have shown that pacemaker implantation in patients with ictal asystole is recommended in patients in whom seizures prove refractory to either anti-epileptic drugs alone, or after combination with neurosurgical therapy [15], as shown in Fig. 25.5. On the other hand, Kohno et al. have reported in a long-term follow-up study that cardiac pacing may not be necessary after successful anti-epileptic drug therapy [16]. Further study is needed to ascertain the optimal treatment strategy, but an initial conservative (i.e., medical management and reserving pacing until later) approach seems prudent at this time.

25.7 Conclusions

Documented asystolic pauses on the ECG in syncope patients may be due to not only primary cardiogenic causes (e.g., sinus node disease, atrioventricular (AV) block), but also reflex syncope and ictal asystole. Primary cardiac causes of symptomatic bradycardia in syncope are a strongly recommended Class I indications for cardiac pacing. However, asystolic pauses secondary to vasovagal syncope or ictal asystole are still weak Class IIb indications for permanent pacemaker implantation. Careful assessment of the differential diagnosis should be made in patients with syncope associated with documented asystolic pauses. In patients with ictal asystole, anti-epileptic drug therapy or neurosurgical therapy are highly effective for the prevention of seizures and ictal asystole. Consequently, cardiac pacemaker implantation should be reserved for instances in which anti-epileptic drugs and/or surgical treatment fail.

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Chapter 26

Cardioneuroablation for Cardioinhibitory Vasovagal Syncope



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26.1 Introduction

The autonomic nervous system (ANS) plays, among its many functions, a critical role in regulating cardiac function (e.g., heart rate, stroke volume) and systemic blood pressure on a beat to beat basis in health. In disease states, on the other hand, pathological changes may lead to ANS disturbances at various levels of the cardiac neuraxis and contribute to increased risk for heart failure, cardiac arrhythmias, and sudden cardiac death [1–4]. Additionally, transient, presumably not related to structural disease, alterations of autonomic cardiovascular control may result in enhanced susceptibility to hypotension and syncope.

As knowledge of the anatomy and function of the major cardiovascular neural connections in humans has advanced, there has been a growing appreciation of the potential for adverse intermittent and self-resolving ANS changes to trigger cerebral hypoperfusion leading to syncope. In such cases, the principal cause is reduced cardiac output due to cardiac arrhythmias (usually marked bradyarrhythmias, but occasionally tachycardias) or vascular dilation (primarily causing decreased venous return), or very often both.

In this chapter, we briefly describe the various elements of the cardiac neuraxis, the associated anatomical targets in various cardiac diseases, as well as assessment of the status of ablative neuromodulatory therapies with a particular focus on vasovagal syncope (VVS) and paroxysmal AV block.

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26.2 Anatomic Basis of Cardiac Neural Control

The cardiac neuraxis can be considered to comprise three levels [5]:

1. Central nervous system neurons including the preganglionic neurons in the medulla (parasympathetic) and spinal cord (sympathetic) and the modulating higher centers such as the thalamus/hypothalamus, prefrontal cortex, amygdala, hippocampus, and cingulate gyrus.
2. Intrathoracic extracardiac ganglia including the paravertebral ganglia, nodose ganglion and dorsal root ganglia, vagus nerves, sympathetic trunks and the cardiopulmonary nerves and plexi.
3. Intrinsic cardiac nervous system including the ganglionated plexi (GP) found within epicardial fat pads in relation to the atria and ventricles.

In regard to the GPs, five groups of ganglia have consistently been described in relation to the atria. These are mixed (sympathetic and parasympathetic) communication sites with variable anatomy; consequently the results of ablation of these regions may not be predictable (Figs. 26.1 and 26.2). The five GP groups may be summarized as:

1. The superior (anterior) right atrial (RA) GP on the posterosuperior surface of the right atrium at the superior vena cava (SVC)—right atrial junction that also extends anteriorly between the SVC and right superior pulmonary vein,
2. The posterior (inferior) RA GP between the inferior vena cava and the interatrial groove,
3. The superior left atrial (LA) GP on the posterior surface of the LA between the superior pulmonary veins,
4. The posterolateral LA GP which lies anterior and inferior to the left inferior pulmonary vein, and
5. The posteromedial LA GP on the inferior aspect of the posteromedial surface of the LA—the posteromedial LA GP and the posterior RA GP are contiguous with each other across the interatrial groove and also extend into the posterior aspect of the interatrial septum.

An additional five GPs are found in relation to the ventricles: (a) An extensive network of GPs around the root of the aorta further divided into the right, left, anterior, and posterior, (b) The GPs around the origin of the right and left coronary arteries extending up to the bifurcation of the left coronary artery into the left anterior descending and the left circumflex arteries, (c) The GPs around the origin of the posterior descending artery, (d) The GP around the origin of the right acute marginal artery, and (e) The GP around the origin of the obtuse marginal artery [7] (Fig. 26.1).

As a group, the atrial and ventricular ganglia contain parasympathetic and sympathetic efferents, sensory afferents, and local circuit neurons which integrate peripheral and central neural information and mediate local reflexes at the level of the ganglia and thus, as suggested by Armour, constitute the “little brain” of the heart [8].

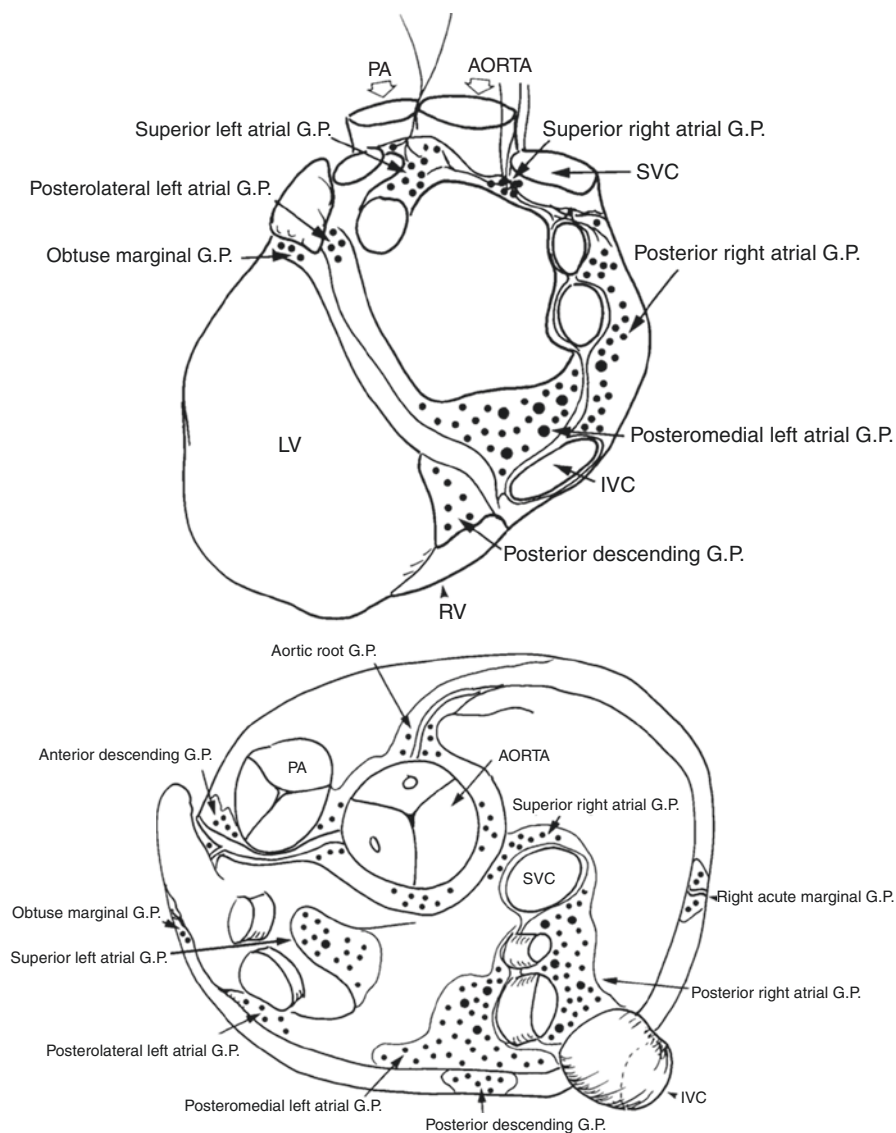


Fig. 26.1 Posterior (above) and Superior (below) views of the heart showing the location of the major cardiac ganglionated plexi (GP). SVC superior vena cava, IVC inferior vena cava, LV left ventricle, RV right ventricle, PA pulmonary artery (Reproduced with permission from Armour JA, Murphy DA, Yuan BX, Macdonald S, Hopkins DA: Gross and microscopic anatomy of the human intrinsic cardiac nervous system. *Anat Rec* 1997; 247:289–298)



Fig. 26.2 Schematic representation of the different atrial ganglionated plexi in relation to the left atrium. *LSPV* left superior pulmonary vein, *LIPV* left inferior pulmonary vein, *LAA* left atrial appendage, *RSPV* right superior pulmonary vein, *RIPV* right inferior pulmonary vein, *SLGP* superior left ganglionic plexus, *ILGP* inferior left ganglionic plexus, *IRGP* inferior right ganglionic plexus, *ARGP* anterior right ganglionic plexus, *LOM* ligament of Marshall (Reproduced with permission from 36. Stavarakis S, Po S. Ganglionated Plexi Ablation: Physiology and Clinical Applications. *Arrhythmia Electrophysiol. Rev.* 2017;6:186–190) [6]

Cardiac preganglionic sympathetic fibers arise from the intermediolateral cell column of T1–T4 segments of the spinal cord and pass through the ventral root of spinal nerves to the paravertebral ganglia, namely superior and middle cervical ganglia, stellate ganglia, and T2–4 ganglia with most fibers synapsing with soma of postganglionic neurons in these ganglia. Postganglionic fibers arising from these ganglia thence pass through cardiopulmonary nerves (CPN) and mix with similar nerves arising from the vagi.

Preganglionic parasympathetic fibers arise from soma in the nucleus ambiguus and dorsal motor nucleus of the vagus and travel through the vagus nerves. These preganglionic fibers then travel through cardiac nerves arising from the recurrent laryngeal nerve (RLN) and from the vagus distal to the origin of the RLN and mix with post ganglionic fibers containing CPN arising from the paravertebral ganglia and the sympathetic trunk to form cardiopulmonary plexi that are distributed along the brachiocephalic trunk, subclavian artery, superior vena cava, and the aortic arch. Nerves arising from these plexi then form the dorsal and ventral cardiopulmonary plexi between the arch of the aorta and the pulmonary artery with nerves arising from these plexi being distributed to all ganglia of the intrinsic cardiac nervous system [9, 10].

Although neurons from intrinsic cardiac ganglia are distributed widely to atrial and ventricular tissues bilaterally without a topographical distribution, these ganglia have their preferential spheres of influence with sinus node function primarily being controlled by the superior RA GP while AV node function is primarily controlled by the posterior RA GP, though some influence is also exerted by other atrial GPs [11, 12].

26.3 Neuromodulation Therapy in Cardiac Disease

Increasing understanding of autonomic cardiac control and its dysregulation in cardiac diseases has led to increased efforts towards identifying strategies for modulating the cardiac neuraxis in an attempt to reverse the altered neural milieu.

Systolic heart failure (i.e., associated with left ventricular dysfunction) is characterized by neurohormonal abnormalities with sympathovagal imbalances, tilted towards sympathetic dominance. Accordingly, betablockers and pharmacological inhibition of the renin–angiotensin–aldosterone axis has been the mainstay in the management of these patients. More recently electrical neuromodulation has been studied to moderate the sympathovagal imbalance, targeting multiple levels of the cardiac neuraxis including the vagus nerve and the spinal cord. Pre-clinical studies of vagus nerve stimulation (VNS) showed significant improvements in ventricular function, reduction in inflammation, and reduction in occurrence of ventricular tachycardia/fibrillation [13–15]. While initial human studies showed similar improvements in ventricular function, subsequent randomized studies have failed to show improvements in ventricular function or survival. More recent studies demonstrating the presence of afferent fibers in the vagus nerve and the adverse effects of recruitment of these fibers during VNS have further improved current understanding of the effects of VNS [16]. Improved understanding of the biophysics of electrical stimulation and the effects of different stimulation parameters on recruitment of various types of nerve fibers is required to further refine this field.

The role of the cardiac neuraxis in regulating atrial and ventricular myocardial electrophysiological characteristics has been well established and pathologic changes occurring at different levels of the cardiac neuraxis have been shown to predispose to cardiac arrhythmias [17]. Modulation of the cardiac sympathetic activity has long been shown to be useful in suppressing ventricular arrhythmias in inherited arrhythmia syndromes such as long QT syndrome and catecholaminergic polymorphic ventricular tachycardia [18, 19]. More recently, the beneficial effects of sympathetic blockade in suppressing ventricular arrhythmias, through cardiac sympathetic decentralization/denervation, thoracic epidural anesthesia, or percutaneous stellate ganglion blockade, have been shown in patients with structural heart disease and ventricular tachycardia (VT) storm [20–22]. Similarly renal artery denervation has been described to be useful in small groups of patients with VT storm. The role of neuromodulation in patients with less frequent episodes of VT is still undefined with further research required to identify easily accessible targets and define optimal neurostimulatory parameters [23].

Neuromodulation in the form of ablation of the intrinsic cardiac ganglia has also been applied in patients with atrial fibrillation (AF) undergoing catheter ablation. The cardiac ganglia have been shown to play an important role in regulating automatic/triggered activity within the pulmonary veins and also influencing the initiation and maintenance of AF [17, 24]. While initial studies demonstrated a benefit of ganglionated plexus ablation in addition to pulmonary vein isolation, the more

recent AFACT study did not reveal added benefits of ganglionated plexus ablation and was instead associated with higher rates of adverse events including major bleeding and need for pacemaker implantation [25, 26]. Other forms of neuromodulation such as low level vagus nerve stimulation have shown benefits in small subsets of patients with AF [27]. Larger clinical studies are required to further evaluate the clinical utility of these effects.

Autonomic modulation to decrease parasympathetic tone has also been attempted in bradyarrhythmias including paroxysmal AV block and sinus bradycardia [28–31]. However, to date, these observations have been limited to case series and small observational studies. Larger studies are needed to better define the population of patients who would benefit from this treatment strategy and delineate the best ablation strategy for such patients before it can be widely adopted.

26.4 Neuromodulation/Cardioneuroablation in Vasovagal Syncope

Pathophysiological mechanisms involved in VVS have been described in earlier chapters. The premise of neuromodulation in VVS is to lower the vagal tone (a high vagal tone forming the presumptive final common pathway for at least the cardioinhibition in VVS), by ablating epicardial intrinsic cardiac ganglia. Although these ganglia contain both sympathetic and parasympathetic fibers, the majority of parasympathetic fibers pass through and synapse within these ganglia before reaching the heart, while a significant proportion of postganglionic sympathetic fibers pass directly to the heart without going through these ganglia; thus the result, assuming uniform GP ablation success, is a predominant parasympathetic denervation when these ganglia are targeted.

Cardioneuroablation for VVS was first described by Pachon J et al. who reported a series of five patients with recurrent episodes of neurally mediated syncope undergoing radiofrequency catheter ablation of intrinsic cardiac ganglia [28]. A combined Fast-Fourier Transform (FFT) spectral guided and anatomically guided approach was used with ablation performed in the regions of the superior right atrial GP, inferior right atrial GP, and the posteromedial GP of the LA from the superior vena cava, the inferior vena cava, and coronary sinus and the left atrium, respectively. All five patients remained free from syncope after a mean period of 9.2 ± 4.1 months of follow-up. A similar positive response to catheter ablation was reported by the same group in a larger cohort of patients ($n = 43$) with “malignant” cardioinhibitory neurally mediated syncope (mean number of episodes = 4.7 ± 2 per patient) who were followed for a longer duration post-ablation procedure. After a mean period of follow-up of 45.1 ± 22 months, only three episodes of syncope were reported in the entire study population, further emphasizing the potential beneficial effects of cardioneuroablation in these patients [32]. Similar results were reported by Sun et al. who followed 57 patients with

Table 26.1 Prospective studies of cardioneuroablation for vasovagal syncope

	Number of patients	Type of VVS	Site of ablation	Approach to cardioneuroablation	Duration of follow-up	Recurrence
Pachon et al. [28]	5	CI	RA + LA	Anatomic + spectral	1 year	0
Pachon et al. [32]	43	CI	RA + LA	Anatomic + spectral	11–91 months	3 (7%)
Yao et al.	10	CI	LA	High frequency stimulation	36 months	0
Sun et al. [33]	57	CI	LA	Anatomic (47) or high frequency stimulation [11]	12–102 months	5 (8.8%)
Hu et al. [34]	115	CI + VD	RA + LA	Anatomic + high frequency stimulation	18 months (median)	9 (7.8%)

CI cardioinhibitory, VD vasodepressor, RA right atrium, LA left atrium

refractory vasovagal syncope undergoing cardioneuroablation [33]. A combined anatomic and high frequency stimulation (HFS) approach was used to guide catheter ablation. At the end of a mean period of 36.4 ± 22.2 months of follow-up, 52 (91.2%) patients remained free of syncope [33]. The same group recently expanded on their initial study and showed a 92.2% syncope/presyncope free survival in 115 patients after a median of 18 months of follow-up [34]. Other groups have reported smaller case series and case reports of cardioneuroablation with promising results [29, 30, 35] (Table 26.1).

26.4.1 Approach to Cardioneuroablation for VVS

Four different approaches have been described to guide catheter ablation of intrinsic cardiac ganglia for VVS:

1. The anatomically guided approach is most frequently employed with ablation performed at presumed sites of location of cardiac ganglia as described above (Figs. 26.1 and 26.2).
2. As noted above Pachon et al. describe a FFT spectrally guided approach to localize cardiac ganglia. In this approach they describe the presence of differences in local endocardial electrograms at sites of location of epicardial cardiac ganglia that can be detected using spectral analysis. They demonstrated a homogenous spectrum with a single dominant frequency of around 40 Hz in normal myocardium while a fibrillar pattern showing a heterogeneous spectrum with several frequencies greater than 100 Hz was seen at sites of location of cardiac ganglia. Of note, a similar fibrillar pattern was also noted at sites of location of the sino-

atrial node and the atrioventricular node thought to reflect the high neural density around these structures [28].

3. In the HFS guided approach, high frequency stimulation (20 Hz, 10–20 V, pulse width 5 ms) at likely sites of cardiac ganglia is performed. The presence of cardiac ganglia is indicated by the occurrence of a vagal response defined by a transient ventricular asystole, AV block, or a 50% increase in R-R interval [33].
4. More recently, Aksu et al. described an electroanatomic approach to cardioneuroablation in which they use the presence of fractionated endocardial electrograms to identify location of cardiac ganglia and guide ablation [35].

Whether one or other of these approaches to identify GP target sites is superior to the others is currently unknown. Further comparative evaluation in clinical studies is needed.

26.4.2 Future Perspectives for Cardioneuroablation in VVS

While results of a number of single center observational studies are encouraging, several questions remain unanswered. Firstly, cardiac ganglia are known to contain local circuit neurons which are capable of processing local reflexes that dynamically control cardiac indices. Potential adverse effects of ablation of these neurons as part of ganglia ablation remain to be elucidated. Secondly, these ganglia lie epicardially within protective fat pads which lowers the success of any ablation strategy. The degree to which radiofrequency ablation delivered from the LA/RA endocardium can disrupt these ganglia needs to be further characterized. Epicardial approaches are similarly limited by the protection offered by fat covering ganglia tissue. Potentially new catheter designs and/or energy delivery methods will need development. Third, nerves are known to be capable of remodeling and re-growing following injury. The extent to which nerves within these ganglia sprout, regenerate, and re-establish synaptic connections needs to be better understood. It is possible that abnormal nerve sprouting could prove pro-arrhythmic. Fourth, end points for ablation are not yet clearly established. While some groups have suggested the use of electrophysiological parameters such as shortening of the R-R interval, AH interval, or A-V Wenckebach cycle length, others have suggested abolition of an HFS-induced “vagal response” as a targeted end point [29, 34]. More recently, Pachon et al. described a technique for vagus nerve stimulation to identify an end point for cardiac ganglia ablation [36]. The clinical utility of each of these end points need to be further evaluated. Finally, while all ganglia sites have been targeted so far, the effects of ablation at individual sites on clinical outcomes need to be studied to further refine treatment strategy.

Importantly, current evidence in favor of neuromodulation is derived from observational studies and case series, thus necessitating caution in interpreting the reported results. Though the duration of follow-up in some of these studies is impressive, their non-randomized nature is an important limitation. The lack of a

control group and absence of blinding of both patients and investigators raises the possibility of bias and placebo effect. Well-designed randomized controlled studies should be the next step in the evaluation of this novel treatment strategy before its wide spread adoption for a disease entity which currently otherwise has limited treatment options.

26.5 Conclusion

That autonomic neural regulation is crucial in regulating cardiac inotropy, chronotropy, and dromotropy has been well known for many decades; however, only recently has the possibility of altering the autonomic inputs to improve health become of increased interest. Pathologic neural changes occurring in various cardiac diseases have been shown to increase the risk of cardiac arrhythmias and sudden cardiac death while also contributing to the progression of the underlying cardiac disease. These observations have ushered in the era of neuromodulation for favorably altering the natural history of various cardiac disorders including ischemic heart disease, heart failure, and cardiac arrhythmias.

While initial reports of successful outcomes of cardioneuroablation in VVS are exciting, this enthusiasm is tempered by the absence of randomized studies. Further studies are required to verify these results and establish optimal strategies of cardioneuroablation before its widespread adoption in the clinical management of this challenging cohort of patients.

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Chapter 27

Driving and Flying: US and European Recommendations



Scott Sakaguchi and Wayne O. Adkisson

27.1 Introduction

When advising patients with syncope or risk for syncope regarding their suitability for driving or piloting aircraft, physicians must assess the individual's risk for syncope recurrence and consider the risk posed to others when a patient drives or pilots an aircraft. Professional cardiac societies have published recommendations for syncope patients and driving [1–6]. A few countries have detailed guidelines for licensing of drivers with medical issues [7–11]. The European Union (EU) has proposed uniform minimum standards of physical and mental fitness to drive [9, 12, 13]. Differences among recommendations reflect the state of the literature at the time of writing, cultural differences between populations, and the individual opinions of the writing committees. This chapter will review medical and legal recommendations for driving or flying by a patient with a prior syncope, or with an implantable cardioverter defibrillator (ICD) with or without syncope. Other reviews of driving with a history of arrhythmias, syncope, and/or ICDs have appeared and the reader is advised to consider examining those reports as well [10, 12, 14–16].

27.2 Driving

27.2.1 Legal Aspects

Physicians must be aware of the laws relevant to their region of practice. The United Kingdom (UK) Driver and Vehicle Licensing Agency (DVLA) publishes detailed guidelines regarding syncope based on diagnosis and presentation (Tables 27.1 and 27.2) [8].

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Table 27.1 Syncope

UK DyLA [8] (legal guidelines)		European Professional Organizations ESC [1] EHRA [5] (medical guidelines)	European Commission [13] (legal guidelines)	US Professional Organizations AHA/HRS [2, 3, 6] (medical guidelines)
<i>Neurocardiogenic syncope</i>				
<i>Group 1</i>	<i>Group 2</i>	<i>Group 1 [1]</i>	<i>Syncope during severe illness or injury with volume loss and/or extreme vagal activity. Syncope during medical procedures. Group 1 and 2: no restrictions Isolated VVS or CSS Group 1 and 2: no restrictions Micturition or defecation syncope, even if recurrent GROUP 1 and 2: no restrictions Recurrent VVS or CSS, or severe situational syncope due to cough or swallowing Group 1: 6 months Group 2: CANNOT drive</i>	<i>Group 1 [6]</i> VVS None in past year: no restriction 1–6 episodes/year: 1 month >6 episodes/year: CANNOT drive until symptoms resolved CSS Treated with PPM: 1 week Untreated: CANNOT drive <i>Group 2 [3]</i> VVS Mild: 1 month Severe, treated: 6 months Severe, untreated: CANNOT drive CSS Mild: no restriction Severe, treated, controlled: 1 month Severe, treated, uncertain control: 6 months Untreated: CANNOT drive
	<i>Isolated Typical VVS While standing: may drive While sitting: may drive if trigger is avoidable, ELSE no driving until risk is <20%/year Recurrent Typical VVS While standing: may drive While sitting: no driving until risk is <20%/year Other syncope with avoidable trigger or reversible cause While standing: may drive While sitting: 4 weeks Cough syncope Isolated: 6 months Recurrent: 12 months for multiple episodes in 5 years</i>	<i>Isolated No restrictions unless it occurred during driving Recurrent/Severe After successful treatment is established Group 2 [1] Isolated No restrictions unless it occurred while driving or without prodrome Recurrent/Severe CANNOT drive unless effective treatment established</i>		

<i>Unexplained syncope</i>			
<i>Group 1</i>	<i>Group 2</i>	<i>Group 1 [1]</i>	<i>Group 1 [6]</i>
“Unexplained syncope, including syncope without reliable prodrome” <i>Isolated</i> 6 months <i>Recurrent</i> 1 year	“Unexplained syncope, including syncope without reliable prodrome” <i>Isolated</i> 12 months <i>Recurrent</i> 10 years	No restriction unless absence of prodrome, occurrence during driving, or presence of severe structural heart disease. If yes, after diagnosis and therapy established <i>Group 2 [1]</i> After diagnosis and appropriate therapy is established	Syncope of undetermined etiology”: 1 month <i>Group 2</i> Not discussed
“Cardiovascular but excluding typical syncope” ^a While standing or sitting: 12 months <i>Isolated</i> “CV, but excluding typical syncope” Cause identified and treated: 4 weeks Cause not identified: 6 months <i>Recurrent</i> “Recurrent CV but excluding typical VVS”: 1 year “if there are factors that would lead to an increased risk of recurrence”.	“Cardiovascular but excluding typical syncope” ^a While standing or sitting: 12 months <i>Isolated</i> “CV, excluding typical syncope” Cause identified and treated: 3 months Cause not identified: 12 months <i>Recurrent</i> “Recurrent CV but excluding typical VVS” Cause identified and treated: 3 months Cause not identified: 2 years	Syncope of unknown cause (as well as syncope of presumed reflex origin) with no evidence of underlying heart disease or association with a disposition for arrhythmia: <i>Same recommendations as neurocardiogenic syncope</i>	

Selected cardiology guidelines and selected legal statements. Time periods indicate restriction from driving with no recurrence of symptoms or arrhythmia, on therapy UK United Kingdom, *DVLA* Driver and Vehicle Licensing Agency, *ESC* European Society of Cardiology, *EHRA* European Heart Rhythm Association, *US* United States, *ACC* American College of Cardiology, *AHA* American Heart Association, *HRS* Heart Rhythm Society, *VVS* vasovagal syncope, *CSS* carotid sinus syncope, *CV* cardiovascular, *PPM* permanent pacemaker

“For a solitary episode the document lists “Cardiovascular, excluding typical syncope,” while in the section on recurrent episodes the document lists “Recurrent cardiovascular but excluding typical vasovagal syncope”

Table 27.2 Defibrillator patients, with/without syncope

UK DVL A [8] (legal guidelines)	European Professional Organizations ESC [1] EHRA [5] (medical guidelines)	European Commission [13] (legal guidelines)	US Professional Organizations AHA/HRS [2, 3, 6] (medical guidelines)
<i>Implantable cardioverter defibrillator patients</i>			
<i>Group 1</i>	<i>Group 1</i> [5]	<i>Group 1</i>	<i>Group 1</i>
New ICD implant	New ICD implant	New ICD implant	New ICD implant
1° Prevention—1 month	1° Prevention—1 month	1° Prevention—2 weeks	1° Prevention—at least 1 week [2]
2° Prevention—6 months	2° Prevention—3 months	2° Prevention—3 months	2° Prevention—6 months [3]
Any shock and/or symptomatic ATP but no incapacity—6 months	After appropriate ICD therapy—3 months	Appropriate ICD therapy—3 months	Syncope, LVEF <35%, presumed arrhythmia with ICD: 3 months [6]
Any therapy associated with incapacity—2 years	After inappropriate ICD therapy—may drive when measures are taken to prevent inappropriate therapy	Inappropriate ICD therapy—no driving until measures taken to prevent recurrence of inappropriate therapy	(1996 guidelines for appropriate ICD therapy: 6 months [3])
Inappropriate tx, cause satisfactorily controlled—1 month	Patients refusing 1° prevention	<i>Group 2</i>	<i>Group 2</i>
Appropriate tx, subsequently treated with drugs or ablation—6 months	ICD—no restriction	CANNOT drive	CANNOT drive [3]
ICD for VT NOT associated with incapacity—1 month if: VT hemodynamically stable *AND* LVEF >35% *AND* Any VT has RR > 250 ms *AND* Post implant EPS; any induced VT pace-terminated × 2	Patients refusing 2° prevention ICD—7 months		
<i>Group 2</i>	<i>Group 2</i> [5]		
CANNOT drive	CANNOT drive		

Selected cardiology guidelines and selected legal statements. Time periods indicate restriction from driving with no recurrence of symptoms or arrhythmia, on therapy

UK United Kingdom, DVL A Driver and Vehicle Licensing Agency, ESC European Society of Cardiology, EHRA European Heart Rhythm Association, US United States, AHA American Heart Association, HRS Heart Rhythm Society, ICD implantable cardioverter defibrillator, ATP anti-tachycardia pacing, VT ventricular tachycardia, VF ventricular fibrillation, LVEF left ventricular ejection fraction, EPS electrophysiology study, RR R-R interval, PVC premature ventricular contraction, NSVT non-sustained ventricular tachycardia

In contrast, in the United States (US) each individual state determines laws regarding licensing. Some states differentiate between syncope and seizures, while many do not [17]. Following an episode of loss of consciousness, individual states may have a no-driving period that varies between states and may or may not be dependent on a particular medical diagnosis.

Selected professional guidelines and laws for patients with syncope or with an implantable cardioverter defibrillator (ICD) are shown in Tables 27.1 and 27.2. These include examples of legal standards in the UK (last updated 2019) [8], the European Commission (EC, the executive arm of the EU) legal recommendations (2013) [13], combined physician guidelines from Europe (European Society of Cardiology [1] and European Heart Rhythm Association [5]), and physician guidelines from the US (American Heart Association (AHA)/North American Society of Pacing and Electrophysiology (NASPE), 1996 and 2007) [2, 3, 6]. Professional guidelines, written at different times by different organizations, and with different focus, do not necessarily replace older documents. Importantly, drivers and physicians are held accountable to local legal standards if they differ from recommendations offered by medical societies.

The duty of a physician to report a driver with syncope (or any medical condition [e.g., seizure] that may pose a risk to others while driving) to licensing authorities varies among jurisdictions. Some US states require physicians to report patients with syncope to licensing authorities, but most do not [17]. In the UK, it is initially the duty of drivers to notify the DVLA when an illness or injury would have a likely impact on safe driving, but physicians are expected to notify the DVLA if “an individual cannot or will not notify the DVLA themselves” [8]. In contrast, German physicians are not permitted to inform licensing authorities of a patient’s loss of fitness to drive, although in cases of extreme risk it has been held that the physician has a right to report [9].

27.2.2 Private Vs. Commercial Driving

Private and commercial drivers with syncope pose different risks to others on the road. The present chapter will broadly adopt the terms Group 1 (“private”) and Group 2 (“commercial”) drivers. In the US, driving is licensed and regulated at the level of the individual state. Group 2 driving requires a commercial driver’s license (CDL) that is also issued by the individual state but medical clearance is required and the medical clearance is regulated at the Federal level. A CDL is required to operate any combination vehicle weighing 10,001 or more pounds (4536 kg), carries 8 or more individuals (including driver) for compensation, or carries 15 or more individuals not for compensation, or carries hazardous material [18].

The Federal Motor Carrier Safety Administration (FMCSA) regulates commercial driving in the US, and has established a registry of Certified Medical Examiners who conduct examinations of Group 2 drivers. A commercial driver may have “no current clinical diagnosis of myocardial infarction, angina pectoris, coronary insufficiency, thrombosis, or any other cardiovascular disease of a variety known to be accompanied by syncope, dyspnea, collapse, or congestive cardiac failure” [19]. For more specific guidance, the FMCSA assembles a Medical Expert Panel (MEP) to develop recommendations within specific specialties such as cardiology. In the EU,

Group 1 drivers may operate motorcycles, cars, or small vehicles with or without a trailer. Group 2 drivers drive vehicles weighing more than 3500 kg, or having more than nine seats (including the driver) [13].

27.2.3 *Determining “Acceptable” Risk*

A large population-based study in Denmark found that residents with a diagnosis of syncope made in a hospital or emergency department were twice as likely to have a motor vehicle accident (MVA) than the general population [20]. Such data, however, has limited applicability when assessing an individual driver. There is a wide geographic variability in the risk of traffic fatalities. Traffic deaths per 100,000 population are three times higher in the US than in Denmark (12.4 vs. 4); within Europe there is almost a fourfold difference between the “safest” and “least safe countries” [21]. Within the US there is a fivefold range in traffic fatality rates between individual states with 6.77 deaths per 100,000 drivers in Rhode Island (5.51 in the District of Columbia) versus 34.18 deaths per 100,000 drivers in Mississippi [22]. Variability reflects multiple factors including road quality, vehicle construction, percentage of the population driving, licensing requirements for individual drivers, and laws that balance the desire of an individual society to drive versus its desire to drive safely.

A widely accepted mathematical model for assessing driving risk was developed by the Canadian Cardiovascular Society (CCS) [4]. An important conclusion is that a Group 1 driver with a 22% annual risk of sudden incapacitation poses a similar risk to a Group 2 driver of a heavy truck who can legally drive with a 1% annual risk. In this model, the risk of harm (RH) posed by a driver to other road users is assumed to be directly proportional to: TD (the time spent driving), V (the type of vehicle, commercial trucks being more deadly than passenger cars), SCI (the risk of sudden cardiac incapacitation), and Ac (the probability that incapacitation will result in a fatal or injury-producing accident). Mathematically, the model states:

$$\text{Risk of Harm (RH)} = \text{TD} \times \text{V} \times \text{SCI} \times \text{Ac}$$

In the model, Ac is taken to be 0.02. Less than 2% of driver sudden deaths or syncopal spells result in injury or death to anyone other than the driver [1, 3, 23]. Many patients with cardiac syncope have sufficient warning to take steps to avoid an accident. In one series, 87% of patients reported prodromal symptoms prior to syncope [24]. In the Danish study, ICD patients with syncope did not have an increased risk of MVAs, and syncope patients with cardiovascular disease had a lower risk of an MVA than those without [20]. In contrast, 28% of traffic fatalities in the US in 2016 were alcohol-related, and 42% of these fatalities were individuals other than the driver [22]. TD is taken to be 0.25 and 0.04 h for the Group 2 and Group 1 drivers, respectively, assuming that they drive 6 h and 1 h a day, respectively [4]. Based on the difference in fatalities caused by trucks and automobiles in Canada, V was assigned a value of 1 for a truck, and 0.28 for an automobile [4].

In Canada, the driver of a heavy truck can return to driving following an acute myocardial infarction (MI) if he or she is functional Class I, has a negative exercise

test at 7 Mets, has no disqualifying ventricular arrhythmias on ambulatory ECG, and is at least 3 months post infarction. Such an individual could not be assigned a risk of less than 1% of cardiac death in the next year. Thus, this individual who can legally drive a commercial vehicle has an SCI of 1% (0.01) [4].

Then, the RH of a post-MI commercial truck driver who can legally drive is:

$$\begin{aligned} \text{RH} &= \text{TD} \times \text{V} \times \text{SCI} \times \text{Ac} = 0.25 \times 1.0 \times 0.01 \times 0.02 \\ &= 0.00005 \end{aligned}$$

A private driver would pose a similar risk to this truck driver by solving for SCI:

$$\begin{aligned} \text{SCI} &= \text{RH} / (\text{TD} \times \text{V} \times \text{Ac}) = 0.00005 / (0.04 \times 0.28 \times 0.02) \\ &= 0.223 \end{aligned}$$

In summary, a commercial driver in Canada is allowed to drive with a 1% (0.01) annual risk of sudden death 3 months after an uncomplicated acute MI. That driver poses a 0.005% (0.00005) risk of seriously harming another individual (RH) in the course of driving. Using the same RH as an upper acceptable limit, the typical private driver of an automobile may be afforded a 22% (0.223) annual risk of a sudden incapacitating event.

27.2.4 *Vasovagal Syncope and Syncope of Unknown Origin*

27.2.4.1 **Group 1 Drivers: Summary**

Guidelines for driving following vasovagal syncope (VVS) attempt to risk stratify patients. Low-risk features are variously identified and include: a single episode of syncope; episodes with clear, avoidable triggers; episodes that occur only while standing. Such patients are usually allowed to drive without restriction or with a 24-h restriction. Guidelines are less specific for patients who do not meet low-risk criteria, e.g., restricting driving until successful treatment is established (very difficult for infrequent attacks), or recommending observation periods ranging from 3 months [3] to 6 months [13]. Permanent restriction from driving may be advised for severe, untreated VVS [3, 6]. UK guidelines include recommendations for cough syncope that are stricter than VVS. Recommendations for syncope of unknown origin vary widely. A single unexplained episode of syncope may require no driving restriction in Japan [10], or a 6 month restriction in the UK [8]. For recurrent unexplained syncope driving may be suspended for 3 months [4] to one year [8], or until a treatment is established [1, 13].

27.2.4.2 **Group 2 Drivers: Summary**

Recommendations for Group 2 drivers deemed to have low-risk VVS range from no restriction [1, 13] to 3 months [8]. Higher risk patients may be restricted for periods of 3 months [3] to complete restriction [3, 8, 13]. In the US, pacemakers are not

accepted as definite treatment for VVS [25]. Recommendations for an unexplained, isolated episode of syncope may include a suspension of driving for one to 5 years. Driving suspension of up to 10 years [8], or until a treatment is established [1], may be recommended for recurrent syncope.

27.2.4.3 Discussion

Vasovagal syncope (VVS) is the most common diagnosis among patients who pass out while driving, being found in 30–67.5% of patients based on tilt table testing [24, 26, 27]. The prospective trials POST-1 and -2 (Prevention of Syncope Trial) were randomized, placebo-controlled, double blind trials that assessed the effects of beta-blockers and fludrocortisone, respectively, on VVS. Neither intervention was found to significantly reduce recurrent syncope. One hundred seventy-four of 418 enrolled subjects had syncope in follow-up. Two passed out while driving, neither sustained or caused injury. The probability of syncope while driving per year was 0.62%, corresponding to a risk of harm of 0.0035%, less than the CCS benchmark of 0.005% [28].

Controlled trials of drugs in VVS have been disappointing [29, 30]. Currently, non-pharmacologic management has been front-line therapy for VVS. Most patients with VVS while driving have reported prodromal symptoms and may be able to avoid an MVA [24, 31, 32]. In one study, 101 patients with VVS diagnosed by tilt table testing were treated with education and no pharmacologic intervention. The median frequency of syncope prior to tilt testing was 0.3/month and decreased to 0.03/month after tilt testing and counseling [33].

The occurrence of syncope while driving may not imply higher risk than syncope unrelated to driving. In a study of consecutive patients who presented with syncope of any cause, the actuarial recurrence rate of any syncope during 1 year was 14.1% in patients with syncope while driving and 17.0% in patients whose syncope was not related to driving. Among patients who had an episode of syncope while driving, the risk of a recurrent syncopal episode while driving was 0.7% at 6 months and 1.1% at 12 months. The most common cause of syncope was reflex (37.3%), followed by cardiac arrhythmias (11.8%) [24]. In spite of these findings, syncope that occurs while driving causes concern so that, for example, ESC guidelines advise no restriction (Group 1 or 2 drivers) for a single/mild episode of reflex syncope “unless it occurred during driving” [1].

The extensive UK guidelines for syncope illustrate the difficulties in writing, and following, guidelines. On one hand, “general” guideline statements offer room for physician interpretation and clinical judgment but may leave physicians adrift in difficult cases. For example, for VVS that occurs without an avoidable trigger while sitting, Group 1 drivers may return to driving when the risk of recurrence is judged to be <20%/year. It is much more onerous, however, with a Group 2 driver who must be judged to have a recurrence risk of <2%/year. On the other hand, very “specific” guidelines may be difficult to apply in complex cases. For example, depending on whether a Class 2 driver in the UK is judged to have recurrent “unexplained

syncope, including syncope without reliable prodrome” versus “recurrent cardiovascular but excluding typical vasovagal syncope” for which “no cause has been identified” (potentially questioning the “cardiovascular” nature of the diagnosis) will lead to the driver’s license being refused or revoked for 10 years or 2 years, respectively [8].

CCS recommendations are notable in that, in the absence of structural heart disease, driving recommendations for syncope of unknown origin are the same as for VVS. Three groups of investigators reported that patients with undiagnosed syncope had identical outcomes regardless of whether they had positive or negative tilt table tests, so the groups were combined for purposes of driving recommendations [4]. More recent findings were, if anything, even more optimistic; in the 18% of syncope patients whose etiology remained undiagnosed in the study by Sorajja et al., their incidence of syncope recurrence was roughly half that of patients with VVS [24]. Based on one study of 209 patients with recurrent VVS who continued to drive after their initial episode, only 5 of 6988 syncope spells occurred while driving over the course of 1534 patient/years, with only 2 of the 5 episodes resulting in injury [34]. While acknowledging the limitations of a small, single center study, the authors calculated the value of A_c (the risk of VVS or, by presumption, unexplained syncope causing an injury in an MVA) to be $2/6988$ or 0.0003 , indicating a low risk (lower than the $A_c = 0.02$ used in the Canadian model) [4].

27.2.5 Ventricular Arrhythmias and Defibrillators

27.2.5.1 Group 1 Drivers: Summary

Following implantation of a secondary prevention ICD, i.e., following symptomatic ventricular tachycardia (VT) or ventricular fibrillation (VF), guidelines recommend no driving for 3–6 months. Following implantation of a primary prevention ICD, guidelines recommend 1 to 4 weeks for recovery from the procedure and assurance of stable lead characteristics. Guidelines vary following appropriate ICD therapy or symptomatic ventricular arrhythmias: 3 to 6 months of no driving is often prescribed, but observation may be as short as 4 weeks in Australia [7] or as long as 2 years in the UK if ICD therapy was associated with incapacitation; a patient may drive sooner if the arrhythmia is effectively treated [8]. Individual guideline or consensus documents may include recommendations for specific situations such as idiopathic VT or NSVT, but they will not be discussed in detail here.

27.2.5.2 Group 2 Drivers: Summary

There is widespread agreement among regulatory authorities that commercial driving is disallowed for patients at risk for ventricular arrhythmias, whether or not they have an ICD [2, 5, 8, 19].

27.2.5.3 Discussion

Patients with VT/VF and ICD patients have gained considerable attention as to their safe operation of a motor vehicle. Multiple studies have shown that immediately following an episode of VT/VF, patients are at increased risk for a recurrent event, and that risk decreases over time [3, 15, 35] allowing most Group 1 drivers to resume driving after their risk of syncope or cardiac arrest has decreased sufficiently. Not all VT/VF events occur while driving, and those that do may not result in an MVA or casualties. Of note, patients with identified cardiac risk often adopt safer driving habits. Patients frequently report driving less and/or more carefully after ICD implant [36–38]. As previously noted, Danish ICD patients with syncope did not have a higher risk of MVAs than the general population [20].

The incidence of syncope and/or presyncope associated with VT/VF and/or ICD therapies has been reported to range between approximately 15–40% [35, 38–43]. An early report of 15% incidence of loss of consciousness (LOC) or sudden death associated with ICD shocks is likely an underestimate because devices of the time did not have stored electrograms so that inappropriate shocks could not be excluded [42]. Two studies reported an incidence of syncope or near-syncope ranging from approximately 30–35% [40, 41], and subsequent analyses of driving risk have used this range [35, 44, 45].

In a study of 2786 Dutch patients with primary and secondary prevention ICDs, the time to first and second shock were analyzed. Anti-tachycardia pacing (ATP) was not analyzed because the incidence of syncope associated with VT and ATP has been reported to be low [45]. Based on a presumed 31% incidence of syncope with an appropriate shock [41], the annual RH was calculated following initial implant and first shock. Following initial implant, both primary and secondary prevention patients had a predicted RH that was below the RH threshold of 5 per 100,000, implying that both groups could be allowed to resume driving immediately following implant [45]. Following a first appropriate ICD shock a primary and secondary prevention patient had a sufficiently high risk of syncope that they should be restricted from driving for 2 and 4 months, respectively. The calculated RH for Group 2 drivers was high enough to support permanent driving restriction [45].

More recently, in the prospective Multicenter Automatic Defibrillator Implantation Trial: Reduce Inappropriate Therapy (MADIT-RIT) study, in which syncope was a pre-specified end-point, 17% of shocks were associated with syncope [43]. Subsequently, a large study of 14,230 patients in a remote monitoring program who received an ICD shock confirmed older studies that the risk of a second shock decreased in the subsequent months. Applying their data to the Canadian model the authors estimate that if the risk of syncope with appropriate ICD shock is 32% (based on prior studies [40, 41, 45]), then patients could safely drive after abstaining 4–6 months following an initial ICD shock. However, if the MADIT-RIT data is indicative of a more “contemporary” risk of syncope with appropriate ICD shock that is only 17%, then the driving restriction could be reduced to 1 month [35]. Even if the lower incidence of syncope with ICD shock is confirmed, however,

the MADIT-RIT study also noted that patients have syncope independent of ICD shocks and that 61% of syncopal spells were non-arrhythmic in etiology [43].

Additional insights may refine risk stratification in the future. The presence of syncope with an index VT event may be predictive of future syncope. Of 26 ICD patients with VT and syncope, 18 had recurrent VT, 12 with syncope; of 50 patients with initial VT without syncope, 36 had recurrent VT of whom only 1 had syncope [39]. The occurrence of an initial ICD therapy predicts a higher risk of future therapies [41]. Extending this observation, a retrospective analysis of 2255 patients in a multicenter post-market study examined up to three occurrences of appropriate ICD therapies. Each appropriate therapy increased the probability of a subsequent appropriate therapy, with each occurring at a shorter time interval. Moreover, a patient who required a shock for the first episode of a ventricular arrhythmia was three times more likely to have a second ICD therapy than if the first episode had been successfully terminated by ATP [44].

An interesting, prospective study on the triggers of arrhythmias examined the probability of receiving an ICD shock during and after driving among 1106 patients. About 70% had a secondary prevention ICD. The relative risk for an ICD shock for VT/VF during the period of driving and 1 h after driving was 2.24 compared to other times. Surprisingly, however, further analysis showed that the increased risk was concentrated in the 30 min after driving and that the risk of VT/VF was not significantly increased during driving [46]. These findings contributed to the EHRA recommendation that the restriction for private driving after a life-threatening arrhythmia be shortened from 6 months to 3 months [5].

It is clear that Group 1 patients continue to drive even when advised not to drive [36–38]. In spite of this, reported accident rates are low. Among 295 patients in the Antiarrhythmics Versus Implantable Defibrillators trial, 8% received a shock while driving; none resulted in an MVA [36]. In a single center study of 171 patients who continued to drive after a secondary prevention ICD, 8 patients had an ICD shock while driving, none had an MVA [38]. In a multicenter prospective study of 275 non-commercial drivers with ICDs (mean follow-up of 26.5 ± 4.5 months), 8 patients received a shock while driving (4 inappropriate), 5 resulting in MVA with no serious injuries or fatalities [37].

An inappropriate ICD therapy could cause an MVA by inducing a malignant arrhythmia, or by the therapy itself, particularly a shock, disrupting a patient's concentration while driving. One retrospective study suggests that such a risk is low: 4089 ICD patients received 772 inappropriate therapies (ATP or shock) that induced 5 episodes of VT and 12 episodes of VF. Two patients developed syncope from VF and a third patient developed syncope due to rapid AF. One patient received a shock while driving but did not have syncope or an MVA. The calculated RH to others from an inappropriate therapy causing syncope was 0.11 and 0.12 in 100,000 for primary and secondary prevention patients, respectively; less than the 5 in 100,000 benchmark (0.005%) [16]. Furthermore, in the previously mentioned Dutch study, if the incidence of syncope with an inappropriate ICD shock was assumed to be 32% (the same as the presumed incidence of syncope with an appropriate shock), the calculated RH was sufficiently low to allow immediate resumption of driving [45].

27.2.6 Other Arrhythmias Causing Syncope [3, 4, 6–9, 11, 13]

Sinus node dysfunction or AV block may cause impairment of consciousness that is effectively treated with a pacemaker. Group 1 patients may resume driving 1–2 weeks after implant to allow time for recovery from the procedure and to ensure stable lead function [1, 3, 6]. Group 2 drivers may typically resume driving 4–6 weeks after pacemaker implant [3, 8]. In the US the MEP has advised FMCSA that a pacemaker is not considered to be definitive therapy for VVS [25]. This is based on several randomized controlled trials that showed no benefit, although the topic remains in a state of evolution as discussed in other chapters.

Patients should not drive if they have syncope or impaired consciousness with supraventricular arrhythmias. Guidelines allow driving after demonstrating some degree of “satisfactory control” or “effective treatment”. Minimum observation periods, e.g. 1 month for Group 1 drivers [3], may be specified for pharmacologic therapy. Guidelines may allow shorter observations periods, 2 days to 1 week, following successful catheter ablation [6, 8]. Group 2 drivers may have longer on-treatment observation periods recommended or required, e.g., 3 months for pharmacologic therapy [8]. Following catheter ablation observation periods may be as short as 6 weeks [8].

Patients with syncope or impaired consciousness should not drive with idiopathic VT (i.e., no structural heart disease). Group 1 drivers may be considered for future driving but will generally require longer observation periods on pharmacologic therapy or following ablation than with supraventricular arrhythmias, e.g., 3 months in the most recent ACC/AHA/HRS syncope guidelines [6]. Group 2 drivers with idiopathic VT were not addressed in these guidelines; however, AHA guidelines from 1996 supported commercial driving if there is no recurrence for 6 months on therapy and if there was no impairment of consciousness with VT [3]. ESC guidelines recommend permanent restriction for Group 2 drivers with life-threatening arrhythmias (e.g., inheritable disorders), but allow driving for Group 1 drivers with arrhythmias (life-threatening or not) after successful medical treatment is established. Group 1 or 2 drivers may drive after successful ablation of a cardiac arrhythmia [1].

27.3 Flying/Piloting an Aircraft

Physicians designated to perform medical examinations of pilots are required to deny medical clearance for a broad range of specified diagnoses. Individuals denied clearance are evaluated on a case-by-case basis by the national authority. In the US, clearance is initially denied for any disturbance of consciousness, implanted pacemaker or defibrillator, and a wide variety of arrhythmias. The situation is similar in Europe although a single, explained episode of VVS may be cleared by the examiner. Otherwise, syncope patients in the US and Europe will require cardiology evaluation and review by their respective regulatory agency. Protocols to clear pacemaker patients include observation periods (2 months in the US, 3 months in Europe).

In the US the Federal Aviation Administration (FAA) is the national aviation authority and oversees all aspects of the aviation industry including the licensing of pilots. In Europe each nation has its own regulatory body but, since 2008, the European Aviation Safety Agency (EASA) has been the supreme regulatory body in the European Union (EU). For example, in the UK the Civil Aviation Authority is the aviation regulatory body but, in many respects, acts as the local body on behalf of the EASA. This relationship may change pending the outcome of, and the agreed regulatory circumstances surrounding, the potential UK withdrawal from the EU (Brexit). It should be noted that other countries also use the name Civil Aviation Authority for their respective regulatory agency. In the US, physicians in private practice who are designated by the FAA as an Aviation Medical Examiner (AME) perform the majority of medical examinations for non-military pilots. In Europe such physicians are designated by the EASA as an Aeromedical Examiner (also AME; the terms will be used interchangeably).

In the US, cardiac exclusions are the same for all three classes of FAA medical certificates (covering airline transport to private/recreational pilots), including [1] “disturbance of consciousness without satisfactory medical explanation” and [2] permanent pacemaker [47]. There are no specific references to “vasovagal,” “neuro-cardiogenic” or “reflex” syncope. A 2-month observation period and a cardiac evaluation are required following pacemaker implantation. In the US, the AME may then refer the application to the FAA for further consideration. Patients with “anti-tachycardia devices” and ICDs are also deferred to the FAA, but subsequent approval to fly is unlikely. Other arrhythmia-related diagnoses requiring FAA referral include tachyarrhythmias, and manifestations of conduction system disease. Following radiofrequency ablation procedures (specific arrhythmias not delineated) pilots may be certified if there is no recurrence during a 3-month wait [47].

In Europe the same cardiac conditions are deemed unfit for a Class 1 or Class 2 medical certificate (covering airline transport to private pilots). If the applicant is deemed “unfit” the decision can be reviewed by a medical assessor [48]. A pilot with a single, explained episode of VVS may be considered “fit” by the AME, but recurrent VVS is deemed “unfit.” A “fit” assessment may be considered after 6 months without recurrence and following a cardiac evaluation. Applicants may be limited to fly “as or with a qualified co-pilot” for a period of time. Loss of consciousness without significant warning and “unexplained vasovagal syncope” are assessed as unfit and requires cardiology consultation and referral to the medical assessor [48]. Pacemaker patients are initially considered unfit but may be considered to be fit 3 months after implant in the absence of other disqualifying condition, if they are not pacemaker dependent, and if they meet certain programming and follow-up requirements. An individual with an ICD or a “ventricular anti-tachycardia pacemaker” is deemed unfit. Patients with a history of ablation or pacemaker implant require cardiovascular evaluation and referral to the medical assessor. Other arrhythmias, including sinus node dysfunction, broad or narrow complex tachycardia, conduction system abnormalities and ECGs suggesting inherited disorders require referral to the medical assessor [48].

27.3.1 Determining “Acceptable” Risk: The 1% Rule

The European community developed a model to guide in the medical assessment of pilots, referred to as the “1% rule,” that identified a maximum acceptable risk of pilot incapacitation of 1%/year (flight time plus off-duty time) in a multi-crew environment (e.g., pilot and co-pilot) [49]. The model uses a target all-cause, fatal accident rate for a large aircraft of 1 per 10^7 flying hours. Of these, medical incapacitation should account for no more than 1% (the vast majority of accidents are mechanical failure or pilot error) giving a target of no more than 1 accident due to medical incapacitation per 10^9 flying hours.

A 1%/year risk of incapacitation (10^{-2} /year) is approximately 10^{-6} /h. Only 10% of the flight time is deemed as “critical” (take-off and landing) so a pilot with a 1%/year risk of incapacitation would pose a risk to air safety of 10^{-7} /h. In simulator testing a second pilot recovered >99% of threatened crashes due to incapacitation of the first pilot, giving a final risk of 10^{-9} /h, achieving the target. A subsequent analysis suggests that the 1% rule is unnecessarily restrictive and that a 2% rule would be appropriate [49].

Reviews of flight safety reports may show incapacitation rates >1%/year, but the definition of incapacitation in flight databases is broad. Cardiac events make up only a fraction of the events, and many events (e.g., musculoskeletal or gastrointestinal symptoms) are not sudden or as incapacitating as some cardiac events. In one study, 4.3% of UK pilots were at some time (both in-flight and off-duty) “temporarily unfit” to fly. When “incapacitation” was limited to “a medical event with the potential to affect flight safety” the rate was 0.8%/year [50].

A review of US flight data and FAA medical records from 1995–2015 could not identify reliable predictors for an incapacitating cardiac event [51]. The study identified 23 pilots who experienced inflight cardiac events, of whom 8 had previously identified cardiac pathology. Their cardiac pathology codes were compared with 195,703 pilots who did not have medical incapacitation, including 70,283 pilots with previously identified cardiac pathology.

27.4 Summary

Professional cardiology organizations have compiled guidelines for advising patients if and when they may drive a car or pilot an aircraft following a diagnosis of syncope. Legal jurisdictions have compiled laws governing driving and flying, but the laws range from being very specific to very broad. For driving, medical guidelines have largely adopted a mathematical model for risk stratification such that a private individual driving a passenger car should be allowed to drive if their annual risk of sudden incapacitation is less than 22% because they pose the same risk of harm to others as a commercial truck driver in North America who has been legally allowed to drive with medical conditions that carry no less than a 1% risk of

sudden incapacitation. The aviation literature has adopted a “1% rule” such that commercial airline pilots should have no more than a 1% annual chance of sudden incapacitation. All pilots must be evaluated by a designated medical examiner with specific legal guidelines by which they cannot certify a pilot to fly without referral to their specific national aviation authority.

Conflict of Interest The authors have no relevant conflicts of interest.

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